Sleep and Sensory Processing in Infants at Elevated and Typical Likelihood for Autism

Anna De Laet

100327893

University of East Anglia

School of Psychology

30th September 2024

A thesis submitted in partial fulfilment of the requirements of the University of East Anglia for the degree of Doctor of Philosophy.

Abstract

Undisturbed sleep is important at any age, but especially during development, when sleep is necessary for healthy brain maturation. However, during sleep, the brain continues to receive and process sensory input from the environment, awaking if necessary. The brain needs to achieve the right balance between processing sufficient input and protecting underlying processes from sensory disturbance. This thesis aims to understand the mechanisms that link disrupted sleep and sensory sensitivities, two symptoms that are common in autistic individuals, starting early in development. One potential reason why these symptoms often co-occur is that ineffective gating of sensory input disrupts sleep, though other reasons include sleep difficulties causing sensory issues, or both symptoms sharing an underlying cause. This thesis investigated whether there is support for a causal relationship from sensory processing differences to sleep difficulties, focussing on infancy. First we showed that an objective neural measure of sensory gating predicts sleep onset latency in 10 month-old infants, but not night awakenings (Chapter 2). A first indicator that poor gating of sensory input may drive at least some aspects of sleep difficulties. To further explore causality, we analysed a longitudinal secondary dataset with measurements of sensory profiles and sleep onset and maintenance at 5, 10 and 14 months in infants at typical and elevated likelihood for autism (Chapter 3). We examined the directionality of effects – whether sleep difficulties predict sensory differences or vice versa – but found no evidence for either. Instead we found that infants that woke up frequently at night tended to have heightened sensory profile across the course of the study, indicative of a common underlying mechanism driving both sleep and sensory profiles. Then we conducted an experimental study to assess the effect of sensory input on sleep and the interaction with sensory profiles (Chapter 5). We investigated sleep protective markers, such as slow waves and sleep spindles, and arousibility. Before doing so, we ensured that these measures could be reliably detected in our infant dataset by improving the performance of an automated algorithm originally designed for adults (Chapter 4). We found tentative evidence that sensory input during sleep disrupts sleep spindle production only in infants that are more hypersensitive. We also found that infants with heightened sensory profiles tended to have lower slow wave activity and higher arousal levels, irrespective of the sensory environment. These findings indicate that already early in development sleep and sensory processing are intertwined. We find more support for a common underlying mechanism driving both sleep and sensory differences, rather than sensory differences causing sleep difficulties.

Contents

ABSTRACT II

CONTENTS III

LIST OF FIGURES VI

LIST OF TABLES VIII

ACKNOWLEDGEMENTS IX

INTRODUCTION TO THE THESIS 1

CHAPTER 1. GENERAL INTRODUCTION 3

1.1 SENSORY PROCESSING DURING SLEEP 4
1.1.1 MECHANISMS OF SENSORY (DE-)COUPLING DURING SLEEP 5
1.1.2 SLOW WAVES AND K-COMPLEXES 14
1.1.3 SLEEP SPINDLES 17
1.2 SLEEP IN INFANCY 20
1.2.1 CHANGES IN SLEEP MACRO- AND MICRO-ARCHITECTURE IN INFANCY 22
1.2.2 DEVELOPMENT OF SLOW WAVES AND K-COMPLEXES 23
1.2.3 DEVELOPMENT OF SLEEP SPINDLES 24
1.2.4 EARLY SLEEP AND BRAIN DEVELOPMENT 26
1.3 SENSORY PROCESSING DIFFERENCES AND SLEEP 29
1.3.1 AUTISM 29
1.3.2 THE RELATIONSHIP BETWEEN SLEEP AND SENSORY PROCESSING DIFFERENCES 36
1.4 OVERVIEW OF THE THESIS 41
1.5 THE STUDIES BEHIND THE DATASETS 43
1.5.1 THE BASIS STUDY 43
1.5.2 THE SNOOSE STUDY 43

CHAPTER 2. SENSORY GATING AND SLEEP 46

2.1 INTRODUCTION 47
2.2 METHODS AND MATERIALS 48
2.2.1 PARTICIPANTS 48
2.2.2 MEASURES 49
2.2.3. ANALYTICAL APPROACH 52
2.3. RESULTS 53
2.3.1. SLEEP TRAJECTORY 53
2.3.2. ASSOCIATIONS WITH TACTILE REPETITION SUPPRESSION 56
2.4. DISCUSSION 58

CHAPTER 3. LONGITUDINAL INVESTIGATION OF SLEEP AND SENSORY PROFILES 63

3.1 Introduction **64**
3.1.1 Statistical approaches to capture reciprocal influences 65
3.1.2 Aim and hypothesis 70
3.2 Methods **71**
3.2.1 Participants 71
3.2.2 Measures 71
3.2.3 Statistical Analyses 72
3.3 Results **76**
3.3.1 Descriptive statistics 76
3.3.2 Night Awakenings 79
3.3.3 Sleep Onset Latency 80
3.4 Discussion **81**
3.4.1 The latent variables 81
3.4.2 The within-person reciprocal effects 83
3.4.3. The timeframe 84
3.4.4 The timescale 85
3.5 Conclusion **88**

CHAPTER 4. ADAPTING METHODS FOR DEVELOPMENTAL POPULATIONS 89

4.1 Introduction **90**
4.2 Sleep spindles **91**
4.2.1 Approaches to detect sleep spindles in infancy 91
4.2.2 Development of sleep spindles 91
4.2.3 Sleep spindle detection in the SNOOSE study 94
4.3 K-complexes **103**
4.3.1 Approaches to detect K-complexes 103
4.3.2 Development of K-complexes and detection in infancy 104
4.3.3 K-complexes detection in the SNOOSE study 107
4.4 Summary and conclusion **110**

CHAPTER 5. AUDITORY INPUT DURING AN INFANT NAP AND THE INTERACTION WITH SENSORY PROFILES 111

5.1 Introduction **112**
5.1.1 Sleep protection 113
5.1.2 Sleep disruption 115
5.1.3 Analysis approach 116
5.2 Methods **117**
5.2.1 Experimental model and subject details 117
5.2.2 Study procedure 118
5.2.3 EEG data acquisition 119
5.2.4 Pre-processing and sleep staging 119
5.2.5 Low Threshold from the SP-2 Questionnaire 120
5.3 Time-locked responses to stimulation **121**
5.3.1 Methods 122
5.3.2 Results of time-locked responses 131
5.4 Pre-registered analyses: comparison of the Baseline vs. Stimulation naps **134**
5.4.1 Methods 134
5.4.2 Results of pre-registered analyses 139

5.5 Discussion **145**
5.5.1 Higher LT scores associate with lower spontaneous SWA and K-complexes 146
5.5.2 Arousibility 149
5.5.3 Do sleep spindles decrease in the face of noise? 149
5.5.4 Does the type of stimulation matter? 152
5.6 Implications and conclusion **153**

CHAPTER 6. DISCUSSION **154**

6.1 Summary of findings **156**
6.1.1 Sensory processing measures predict sleep onset and night awakenings 156
6.1.2 Sleeping sensory profiles in a noisy environment 157
6.2 Theoretical implications **159**
6.2.1 Do sensory processing differences lead to sleep difficulties? 159
6.2.2 Lower slow wave activity: Underlying mechanisms and implications for learning 161
6.2.3 Improving measurements and the search for the 'right' methodology 163
6.2.4 Sensory influences on sleep onset and awakenings 166
6.3 Considerations for the study of sleep and sensory processing in infancy **169**
6.4 Future directions **171**
6.5 Conclusion **172**

REFERENCES **174**

APPENDIX A. DESCRIPTIVE STATISTICS BY AUTISM LIKELIHOOD AND DIAGNOSTIC STATUS **218**

APPENDIX B. LOW THRESHOLD QUESTIONS **219**

APPENDIX C. CHAPTER 3: VARIABLE DISTRIBUTIONS AND OUTLIERS **222**

APPENDIX D. TOPOGRAPHY OF SIGMA AND DELTA POWER IN THE PILOT SAMPLE **223**

APPENDIX E. K-COMPLEX LIKELIHOOD S1 AND S2 **225**

APPENDIX F. AI, SWA AND SIGMA ACROSS SLEEP STAGES **225**

APPENDIX G. CHAPTER 5: OUTLIERS **226**

List of figures

Chapter 1

Figure 1.1 Thalamo-cortico-thalamic loop 5

Figure 1.2 EEG activity during different sleep stages 7

Figure 1.3 Sensory gating mechanisms during sleep 8

Figure 1.4 Evoked slow wave 11

Figure 1.5 Synaptic Homeostasis Hypothesis (SHY) 17

Figure 1.6 Sleep spindle characteristics 18

Figure 1.7 Development of sleep and its EEG features in the first year of life 23

Figure 1.8 Examples of K-complexes in adults and infants 24

Figure 1.9 The development of sleep spindle features and brain structures across the lifespan 26

Figure 1.10 Hierarchical framework of sensory processing in autism 31

Figure 1.11 Three possible pathways for the co-occurrence of sensory differences and sleep difficulties. 41

Figure 1.12 The SNOOSE study in action 44

Chapter 2

Figure 2.1 Tactile repetition suppression design and analysis 51

Figure 2.2 Sleep trajectories from 5 to 14 months in infants at EL and TL forautism 54

Figure 2.3 Sleep trajectories from 5 to 14 months based on autism likelihood and – diagnostic status. 55

Figure 2.4 Associations with tactile suppression index (TSI) at the 10-month 57

Chapter 3

Figure 3.1 Cross Lagged Panel Model (CLPM) 68

Figure 3.2 Random Intercept – Cross Lagged Panel Model (RI-CLPM) 69

Figure 3.3 Latent Curve Model with Structured Residuals (LCM-SR) 70

Figure 3.4 CLPM of Low Threshold and Sleep 74

Figure 3.5 RI-CLPM of Low Threshold and Sleep 75

Figure 3.6 LCM-SR of Low Threshold and Sleep 76

Figure 3.7 Sample sizes per variable per timepoint 77

Figure 3.8 Summary of the results of the unconstrained RI-CLPM 80

Figure 3.9 The timescales continuum 86

Chapter 4

Figure 4.1 Development of sleep spindle duration across the first year of life 92

Figure 4.2 Representative examples of sleep spindles in different age groups 93

Figure 4.3 Sleep spindle frequency across development 94

Figure 4.4 Performance of 10 exploratory algorithms 100

Figure 4.5 Linear regressions of sleep spindle density based on visual and automatic detection 101

Figure 4.6 Examples of K-complexes in an adult recording 104

Figure 4.7 Grade of K-complex maturity across development 106

Figure 4.8 Example data of different levels of K-complex maturity *106*
Figure 4.9 Example of slow waves detected by YASA in channel Cz *108*
Figure 4.10 Histogram of the negative peak timings of slow waves relative to S1 and S2 *109*
Chapter 5
Figure 5.1 Study completion of the SNOOSE study *118*
Figure 5.2 Stimuli design *119*
Figure 5.3 Boxplots of Low Threshold in the BASIS and SNOOSE study *121*
Figure 5.4 Morlet wavelet *123*
Figure 5.5 Summary of the analyses steps of time frequency representations *124*
Figure 5.6 Analysis window used for K-complex likelihood. *128*
Figure 5.7 Analysis window used for sleep spindle likelihood. *129*
Figure 5.8 Event Related Potentials in the central channels *131*
Figure 5.9 TFR cluster-based permutation *132*
Figure 5.10 K-complex likelihood results *133*
Figure 5.11 Sleep spindle likelihood results *134*
Figure 5.12 Differences in sleep macro-architecture between the baseline and stimulation nap *140*
Figure 5.13 A. Slow Wave Activity (SWA) in baseline and stimulation condition in sleep stage N3 *141*
Figure 5.14 Interaction between sleep spindle features and condition *143*
Figure 5.15 Association between Activation Index in N3 and Low Threshold *145*
Figure 5.16 Pathway from synaptic dysfunction to sleep difficulties and autism symptoms *148*
Chapter 6
Figure 6.1 Time-frequency sigma peaks (TFσ) *165*
Appendices
Figure A.1 Sigma and delta topography in the pilot sample *223*
Figure A.2 Comparison of the topography of slow and fast sleep spindle activity *224*
Figure A.3 Individual sigma peaks *224*
Figure A.5 K-complex likelihood after S1 and S2 *225*
Figure A.6 AI, SWA and sigma activity across sleep stages *225*

List of tables

Chapter 2

Table 2.1 Characteristics of participants included in data analysis at 5-, 10- and 14-month assessments 49

Table 2.2 Skewness and normality values of sleep onset latency at 5, 10 and 14 months 52

Table 2.3 Sample sizes of the analyses with EEG data per model 53

Table 2.4 Bivariate correlations 56

Table 2.5 Summary of results of the concurrent models and longitudinal models with TSI as a predictor 58

Chapter 3

Table 3.1 Descriptives of the sample 77

Table 3.2 Bivariate correlations 78

Table 3.3 Partial correlations 78

Table 3.4 Model fit statistics 81

Chapter 4

Table 4.1 Comparison between the training and validation datasets 95

Table 4.2 Thresholds of the 10 algorithms of round one 97

Table 4.3 Performance metrics for the 10 exploratory algorithms 99

Table 4.4 Threshold settings of algorithms of round two 100

Table 4.5 Comparison of the performance on the training and validation datasets 101

Chapter 5

Table 5.1 Descriptive statistics per condition 139

Table 5.2 Pearson correlations between repeated measures 139

Table 5.3 Results from linear mixed effect model of slow wave activity 141

Table 5.4 Results from linear mixed effect models of sleep spindle density and sigma activity 142

Table 5.5 Results from linear mixed effect models of sleep spindle frequency, duration and absolute power 143

Table 5.6 Results from the linear mixed effect model of arousal density 144

Table 5.7 Results from the linear mixed effect models of the activation index in N2 and N3 144

Appendices

Table A.1 Descriptive statistics by autism likeilihood and diagnostic status 218

Table A.2 Questions from the ITSP of the sensory sensitivity and avoidance quadrants 0-7 months 219

Table A.3 Questions from the ITSP of the sensory sensitivity and avoidance quadrants 7-36 months. 220

Table A.4 Questions from the SP-2 of the sensory sensitivity and avoidance quadrant 7-36 months 221

Table A.5 Outliers and Winsorized values of Chapter 3 222

Table A.6 Normality, skewness and kurtosis 222

Table A.7 Outliers and Winsorized values of Chapter 5 226

Acknowledgements

They say a PhD is a lonely journey, but that is the opposite of what I have experienced. A major reason for this was the support of my primary supervisor Professor Teodora Gliga. I am so grateful to Teea for always caring, whether it was about the big scientific questions, the noisy data or my vegetable garden. I feel very fortunate to have been guided in my formative years as a researcher by a scientist of such integrity. I will always look back at my PhD experience with fondness, thanks to Teea. I also want to express my deepest gratitude to Professor Rachael Bedford for always being excited about my results, even when they seemed very unexciting to me, and being willing to discuss my endless questions about statistics. I want to thank Professor Alpar Lazar for his invaluable insights on everything sleep related and Dr Nadja Althaus for walking me through how to run so many algorithms. I feel very lucky I had such a wonderful (and large) supervisory team with always someone to turn to.

Throughout the three years of data collection for the SNOOSE study I was supported by an amazing team of students, research assistants and post docs. Thank you to Achilleas Pavlou, Dominic Mclean, Fabiola Ruiz-Castro, Emily Hurst and Guilia D'Avino for all your contributions to the project. A special thank you to Morgan Whitworth for all our shared time testing infants and toddlers in the lab and for his patience and curiosity about that data. I am so excited to see you start your own PhD journey in sleep research. The success of the SNOOSE project was made possible by Hope Fincham. I genuinely cannot imagine a better person to have started this journey with. One minute we would debate in great detail whether we saw REM sleep in a sleep recording and the next we discussed our love lives. That is how to build a friendship.

I dedicate this thesis to friendships. All the friends I have made in Norwich and the friends that encouraged me to move here in the first place have contributed to this PhD in one form or another. In the two weeks of freedom between my arrival quarantine and the second national lockdown, I happened to meet the five most wonderful people, who later became 'the fellowship of the indie'. We created our own PhD cohort, spread across departments. Thank you Dr Marco for the hugs, Dr Amy for being the glue (and for creating the playlist to which I wrote this thesis), Dr Elien for understanding and Dr Andrea for the energy. We started this journey together and will (hopefully) finish it together at graduation. To Dr Duncan Maguire, thank you for letting me tap into your beautiful brainwaves, literally and metaphorically. From your brain I learned what alpha waves look like and that one should always pursue doing what is meaningful, and that it is for you to decide what that is. Although we may have never had that official coaching session, some coaching must have slipped through the cracks anyway.

I am also very grateful for my family who supported me from afar. Thank you to my parents, Peter and Karin, who are always proud no matter what I pursue and for listening to my stories of the funny things that toddlers do in the lab. To my sister Sanne, thank you for inspiring me to read my first book about the brain: “We are our brains”. I feel incredibly lucky to have a sister like Sofie, who is always just one phone call away.

Lastly, I do not know how I would have finished this thesis without Jake Brigham, this aggressive badminton player I met at some point. Jake Brigham is the official sponsor of this thesis by providing an infinite amount of beans, rainy park runs for emotional relief and professional editing services. I am indebted to you for all the times you listened and contributed to my ponderings about baby brains, naps and algorithms, I almost started to believe you found them interesting.

Introduction to the thesis

When we fall asleep, the world around us seems to disappear and we drift between unconscious states and dream worlds. Yet, reality around us does still exist and while we might not always be aware of it, we are still monitoring what is happening within the vicinity of our senses. Luckily we do still monitor the world around us - if we did not, our species might not have survived. A sleeping animal is extremely vulnerable to predation and therefore needs to maintain some vigilance. However, sleep also performs many vital functions necessary for survival (Rasch & Born, 2013; Rechtschaffen, 1998). Some of these processes likely rely on being in a disconnected state, undisturbed by interfering sensory signals. A balance between these two opposing needs has to be achieved during sleep. To do so, a system is in place that selectively tunes into the environment when something important requires our attention, whilst maintaining sleep when input can safely be ignored. Andrillon et al. (2020) introduced the term '*vigilant sleeper*' to describe this phenomenon, though other terms have been used as well, such as '*a standing sentinel*' (Blume et al., 2018) or '*a night watch*' (Tamaki et al., 2016).

Interestingly, the selective tuning into the environment depends on the internal state of the sleeper and the type of environment they live (and sleep) in (Beck et al., 2021; Cordi et al., 2019). In an environment that is perceived as 'risky', an animal might sacrifice deep sleep for increased vigilance. For example, when a dove sees a predator before going to sleep, it will 'peek' more during sleep than usual (Lendrem, 1984). A human sleeper in an unfamiliar environment will also be more vigilant, showcased by the 'first night effect' (Agnew Jr et al., 1966; Tamaki et al., 2016) - sleep is more superficial and prone to disturbance when individuals sleep in an unfamiliar environment, such as in a sleep lab for the first time. High vigilance is then prioritised over deep sleep. The opposite also happens, where deep and restorative sleep is prioritised over sensory connection to the environment following physical or mental exertion. For example, deep sleep improves after physical activity (Park et al., 2021) or after sleep deprivation (Ferrara et al., 1999). Sleep also deepens after a learning experience, promoting memory consolidation (Crupi et al., 2009; Pugin et al., 2015).

Furthermore, across the lifespan, sleep architecture changes, with more and deeper sleep during childhood compared to adulthood (Ringli & Huber, 2011), likely reflecting the need for sleep for learning and brain development. Infants in particular spend large amounts of the day asleep and their sleep patterns as well as brain activity during sleep undergo stark changes in the first year of life (Lenehan et al., 2023). Having sufficient sleep is important at any age, but may be especially important during early development (Henderson et al., 2010; Joseph et al., 2015), when sleep plays a crucial role in brain development by regulating cortical plasticity (Frank et al., 2001; Li et al., 2017), and early sleep predicts behavioural outcomes and mental health later in life (Cook et al., 2020; Jaramillo et al., 2023).

Besides state-like differences that change from day-to-day or over longer developmental periods, there are also trait-like differences in sensory responsiveness to the environment during sleep. Some individuals will always wake up more easily from sensory input than others (Bonnet et al., 1978). Individuals with neurodevelopmental conditions often have sleep difficulties (Cortese et al., 2009; Kamara & Beauchaine, 2020), such as waking up frequently at night and prolonged sleep onset (Deliens & Peigneux, 2019) and these symptoms emerge early in life (MacDuffie et al., 2020), potentially influencing the progression of the condition.

Many autistic individuals experience sensory processing differences, such as poor gating of sensory input, during wakefulness (Chamak et al., 2008; Piccardi et al., 2021), but it is unclear whether this extends to sleep. These sensory symptoms tend to emerge early in development (Guiraud et al., 2011; Kolesnik et al., 2019), together with sleep difficulties (Begum-Ali et al., 2023). While sensory processing differences and sleep difficulties are associated, both in autistic and non-autistic individuals (Appleyard et al., 2020; Lane et al., 2022), it is poorly understood how variation in sensory processing translates into sleep difficulties. One hypothesis is that poor gating or filtering of irrelevant sensory input persists during sleep and interferes with sleep onset and maintenance. Understanding this could help inform the development of appropriate interventions for sleep difficulties in infants with sensory processing differences, irrespective of autism diagnosis.

The main aim of this thesis is to investigate why infants who have altered sensory processing so often also have sleep difficulties. In particular, the idea that sensory differences *lead to* sleep difficulties, due to poor gating mechanisms is explored. First, we ask whether an objective measure of poor gating, and not just subjective rating of a range of infant sensory behaviours, during wakefulness predicts worse sleep initiation and maintenance. Then, to assess causality, two approaches are taken. First, using a longitudinal design, the directionality between sensory processing differences and sleep onset and maintenance is explored in the first year of life, using caregiver reports. Second, using an experimental design, the effect of sensory input on sleep is assessed in relation to an infant's sensory profile. Here we ask whether infants who are scored as highly sensitive by their caregiver have altered sleep using objective sleep measures and whether this depends on the presence or absence or sensory input.

Chapter 1.
General Introduction

Three main topics will be introduced in this chapter. The first part will discuss current theories on mechanisms of sensory (dis)connection during sleep. The second part overviews changes in sleep during development and the importance of sleep in brain development, with a particular focus on the first year of life. Lastly, sensory processing differences in autistic and non-autistic individuals will be covered, particularly focussing on the relationship with sleep. Finally, a detailed overview of the following chapters will be provided.

1.1 Sensory processing during sleep

The flow of sensory information to the cortex gradually decreases when we fall asleep and drastically declines when deep sleep is reached. Whether sensory input reaches the cortex heavily depends on vigilance state and alertness levels during wakefulness (Livingstone & Hubel, 1981). Intracellular recordings in cats demonstrate that during wakefulness 90% of incoming visual input reaches the cortex, which diminishes to 70% during drowsiness and 40% during deep sleep (Coenen & Vendrik, 1972). This reduction in efficiency of sensory processing is called *sensory gating*. Reduced sensory processing and responsivity to the environment are key elements that define sleep, and make it distinct from wakefulness. The gating of sensory input facilitates and protects sleep.

When an external stimulus is propagated from the periphery to the cortex, it inevitably needs to pass the thalamus. That is the case for all sensory modalities except for olfaction, which is the only sense that can bypass the thalamus (Öngür & Price, 2000). From the thalamus, signals are propagated to layer 4 of the primary sensory cortices (see Fig. 1.1). Sensory input is then modulated by neurons in layer 5 and 6, before cortico-thalamic neurons project back to the thalamus. These cortico-thalamic neurons also have axons that project to the thalamic reticular nucleus (TRN) and local thalamic interneurons, which both inhibit thalamic relay neurons. From there, signals are transmitted to higher-order integrative cortical areas and elsewhere in the cortex. This complex thalamo-cortico-thalamic system and all its modulatory input yield gain modulation, adjusting the sensitivity of neurons to sensory input (Ferguson & Cardin, 2020). This process is crucial for the state-dependent modulation of sensory input (Livingstone & Hubel, 1981). So how is the gating of sensory input achieved during sleep?

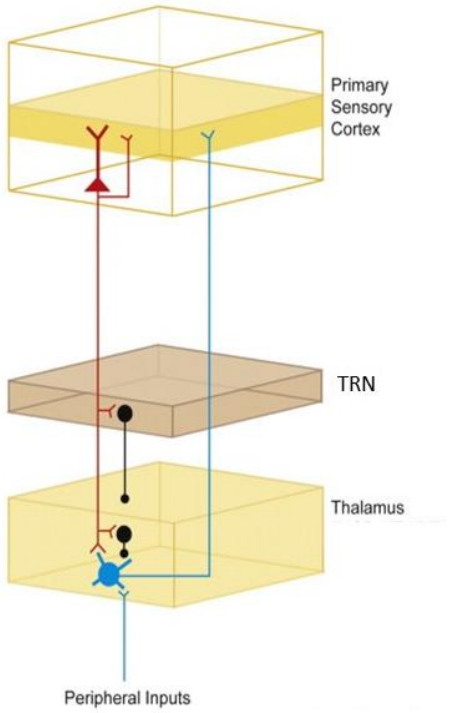

Figure 1.1 Thalamo-cortico-thalamic loop. Sensory input arrives at thalamic neurons (blue), which pass the signal on to Layer 4 of the primary sensory cortices. There the signal is modulated by Layer 5 and 6 neurons and passed back to the thalamus (red). Additionally, axons projecting to the thalamic reticular nucleus (TRN) and thalamic interneurons (black) inhibit thalamic relay neurons. Figure from Briggs & Usrey (2008).

1.1.1 Mechanisms of sensory (de-)coupling during sleep

In 1994, McCormick & Bal proposed a mechanism for sensory disconnection during sleep: *the thalamic gating hypothesis*, a theory that has been influential for many years. McCormick & Bal suggested that sensory input is blocked at the level of the thalamus during sleep, preventing it from reaching the cortex. The thalamus was considered a likely gatekeeper because it receives and propagates most of the sensory input. However, accumulating evidence shows that this thalamic gate can be breached during sleep, even without eliciting a behavioural response. For example, it is possible to encode sensory stimuli during sleep, as evident from evoked potentials in primary sensory cortices to auditory and visual stimuli (Portas et al., 2000; Sharon & Nir, 2018). Furthermore, more complex processing of stimuli is still possible during sleep. The brain is able to discriminate meaningful from non-meaningful stimuli during sleep, a process which goes beyond the encoding of stimuli. For example, two early influential studies demonstrate that a sleeper's arousal threshold - the sound intensity required to wake up - depends on the stimulus saliency, irrespective of the stimulus intensity. In one of these studies, adult sleepers are more likely to wake up when hearing their own name than another name (Oswald et al., 1960). In the second study, new parents were awoken more often from the cries of their own baby than from an unfamiliar baby (Formby, 1967). Even without a behavioural response,

familiar voices and names and emotional tones elicit enhanced neural responses compared to unfamiliar voices and names and unemotional tones (Blume et al., 2017, 2018). Furthermore, the violation of simple auditory rules and arrhythmic facts can (at least partially) be detected (Ruby et al., 2008; Strauss & Dehaene, 2019; Tamaki et al., 2016). For example, sleepers can detect deviations in repetitive auditory input as evidenced by enhanced neural responses, in most sleep stages, but less often in the deepest sleep stage (Ruby et al., 2008; Tamaki et al., 2016). These studies show overwhelming evidence for sensory processing during sleep which would not be possible with strict thalamic gate. However, there are still limitations to the cognitive processes that are possible during sleep and with increasing sleep depth, sensory processing becomes less likely. In fact, the level of sensory disconnection is not equal across sleep states.

During sleep, distinct states are identified based on differences in activity patterns. In mammals, sleep is divided into Rapid Eye Movement (REM) sleep and non-REM (NREM) sleep. In humans, NREM sleep is further divided into N1, N2 and N3, the latter also called slow wave sleep (SWS). See box 1 for more information on sleep stages in humans and an examples of brain activity in each sleep stage. Arousal thresholds are lowest in N1, higher in N2 and REM and highest in N3 (Bonnet et al., 1978; Ermis et al., 2010; Keefe et al., 1971). Because NREM sleep and REM sleep show such fundamentally distinct activity patterns, different gating mechanisms likely operate during both states. As NREM sleep is the focus of this thesis, potential mechanisms of sensory decoupling during NREM will be discussed, but see Andrillon & Kouider (2020) for potential mechanisms during REM sleep.

Box 1. Sleep stages in humans

In humans, sleep is divided into four distinct sleep stages: N1, N2, N3 and REM (Iber et al., 2007). These sleep stages can be distinguished using polysomnography, which includes the measurement of electroencephalography (EEG), electro-oculography (EOG) and electromyography (EMG). See figure 1.2 for examples of EEG activity in each sleep stage.

Sleep stage N1 is the lightest sleep stage, and the transition between wake and sleep. In this stage, alpha waves, that are seen in quiet wakefulness, start to disappear and replaced by slower oscillations amidst low amplitude, mixed frequency background signal. **Sleep stage N2** is marked by the appearance of sleep spindles and K-complexes. The start of N2 is sometimes considered the true onset of sleep. The deepest **sleep stage N3** or SWS, is dominated by large slow waves, with high amplitudes (> 75µV) and low frequencies. Finally, **REM sleep** is characterized my low amplitude, mixed frequency EEG activity that resembles wakefulness. However, it is accompanied by muscle atonia and characteristic rapid eye movements. Sometimes sharp sawtooth waves and theta waves can be seen in the EEG signal, which indicate the sleeper is in REM sleep. Typically, a sleeper cycles through all sleep stages in cycles of 90 min, with more REM sleep towards the end of the night and more SWS in the first half of the night.

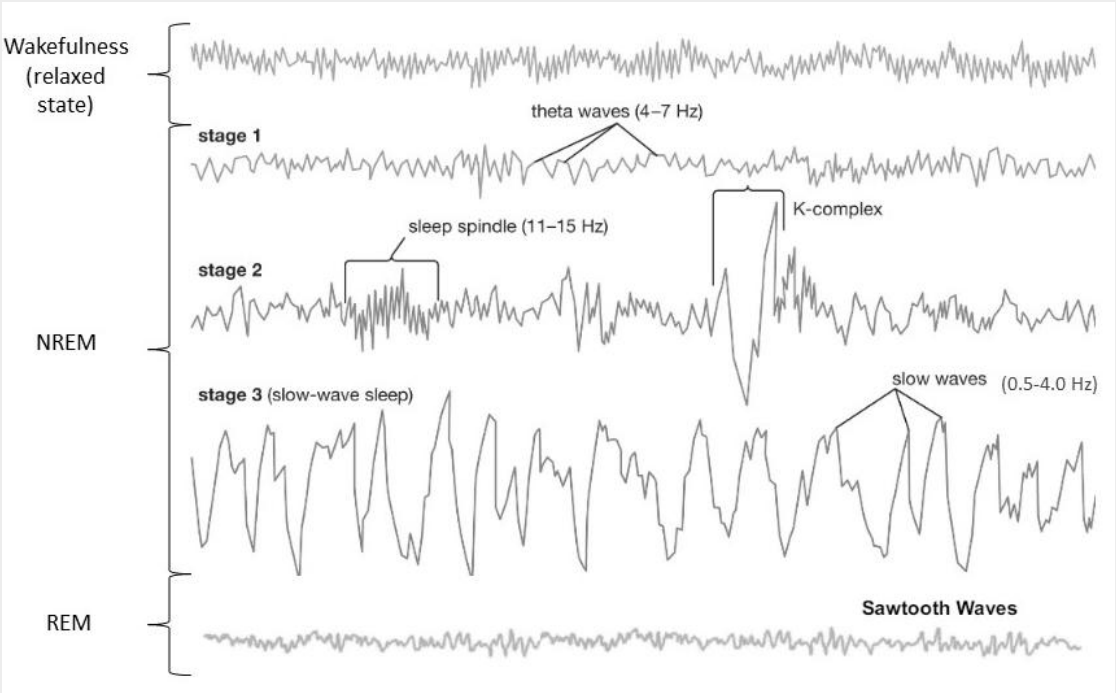

Figure 1.2 EEG activity during different sleep stages. Figure adapted from Britannica (2024) and Dutt et al. (2023).

Due to the accumulating evidence that the thalamic gate can be breached during sleep, a new gating mechanism was proposed, the *cortical gate* (Esser et al., 2009), as a complementary mechanism to a partial thalamic gate (see Fig. 1.3). This was based on observations of cortical connectivity across different vigilance states. Direct stimulation of the cortex by transcranial magnetic stimulation (TMS) shows that during NREM sleep the effective connectivity between cortical regions declines and induced activity is limited to the area of stimulation (Massimini et al., 2005). During wakefulness in contrast, activity rapidly spreads to other cortical regions. The decline in connectivity during NREM sleep, and therefore the diminished propagation of signals between regions, could explain the loss of responsiveness to the environment, whilst also explaining occasional evoked activity seen in the cortex. What is it about NREM sleep that induces this reduction in connectivity?

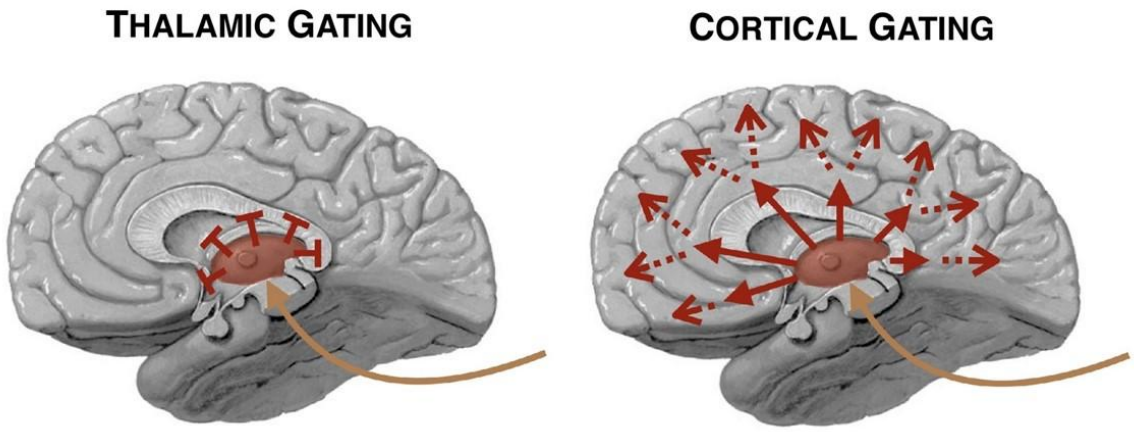

Figure 1.3 Sensory gating mechanisms during sleep. The thalamic gating hypothesis suggests that sensory input is gated on the level of the thalamus. The cortical gating hypothesis suggests that the breakdown of functional connectivity during NREM sleep explains the partial sensory disconnection. Figure adapted from Andrillon & Kouider (2020).

During NREM sleep, and in abundance during N3, the activity pattern is dominated by large slow waves (SWs), which have a frequency of 0.5-4 Hz (See box 1). The large SWs visible in the scalp EEG result from synchronized firing patterns across neural networks. This is due to individual neurons that alternate between active (or ON or up) states and inactive (or OFF or down) states in cycles of 1 Hz, called the slow oscillation or slow rhythm (Timofeev et al., 2020). When large amounts of neurons exhibit the slow oscillation synchronously, SWs appear in the scalp EEG signal. The 'up states' refer to the resting membrane potentials of neurons which are depolarized. In a depolarized state, neurons are slightly more positively charged on the inside, making it easier for a neuron to fire. In contrast during 'down states', membrane potentials are hyperpolarized, meaning they are more negatively charged on the inside, which prevents the neurons from firing (Steriade et al., 1993). During the up

states, neurons fire in bursts, which can both be inhibitory or excitatory. The terms up- and down-states are more often used when referring to intracellular processes, while active or ON and inactive or OFF are commonly used relating to neural firing patterns (Adamantidis et al., 2019). SWs reflect bi-stable dynamics of the brain, where active states are inevitably followed by inactive states. How bi-stability exactly reduces cortico-cortical communication and the effective breakdown of connectivity in the cortex is debated. Rosanova & Timofeev (2005) suggest that the inevitable down state that follows an up state interrupts signal transmission and causes the breakdown of functional connectivity during periods of high bi-stability. Indeed, during a slow wave down state, stimuli can still elicit responses in primary cortices, but signal propagation in higher cortical areas is particularly affected (Schabus et al., 2012). However, Esser et al. (2009) argue that effective communication between cortical areas happens on a shorter timescale than a SW, therefore the transition from an up- to downstate would not truly interrupt signal transmission between cortical areas. Esser et al. suggest that additional mechanisms have to be in place to achieve the reduced effective connectivity. Through computational modelling, they find that the most likely mechanism that creates the cortical gate during SWS is an increase in the ratio of evoked inhibitory to excitatory synaptic responses, which are the consequence of reduced levels of arousal promoting neuromodulators, such as acetylcholine, during SWS.

That SWs de-couple the sleeper from their sensory environment is supported by the fact high slow wave activity (SWA) is related to high arousal thresholds (Neckelmann & Ursin, 1993) and the higher SWA before a stimulus, the less likely a behavioural arousal will follow (Hayat et al., 2020). SWs are therefore a marker of sleep depth and sensory disconnection. SWs determine the extent to which an incoming stimulus is processed and can therefore be considered as a passive form of sleep protection. I will refer to these SWs as *spontaneous*, in contrast with *evoked* SWs that are elicited by sensory input, actively promoting sleep over wakefulness. The factors that determine the amount and strength of spontaneous SWs will be discussed further in section 1.1.2.

External stimulation can on the one hand disrupt sleep by causing an awakening, but on the other hand it can also promote sleep by enhancing SW production. Bellesi et al. (2014) propose a mechanism in which SWs are enhanced through acoustic stimulation. They suggest that just like during wakefulness, auditory stimulation can activate ascending pathways. For a mild stimulus, only parts of the ascending pathways are activated, while an intense stimulus could fully activate the ascending pathways, resulting in an arousal or full-blown awakening. Issa & Wang (2011) indeed find that stimulus intensity affects the processing of sensory input differently during SWS compared to wake. Quiet sounds evoke weak responses in the primary auditory cortex during SWS, much weaker than during wakefulness. However, for loud sounds, neurons are activated similarly during SWS and wake.

According to Bellesi et al. (2014), partly activating the ascending pathways, and thus not arousing the sleeper, still leads to depolarization of many cortical neurons. Due to the bi-stable dynamics during sleep, synchronous depolarization will induce a large hyperpolarization. This leads to an enhanced slow wave with a larger amplitude and steeper slope, that is more widely distributed than a spontaneous slow wave. Indeed, when a stimulus is presented during the up state of a SW, which is the depolarized state, it can induce a train of SWs (Ngo et al., 2013), which promotes and deepens sleep. However, during the down state of a slow wave, an incoming stimulus does not enhance SWs. Therefore, the fate of an incoming stimulus and whether it promotes or disrupts sleep is highly dependent on the ongoing brain activity at the time of stimulus presentation, in addition to the properties of the stimulus, such as its intensity and saliency.

K complexes. Besides trains of SWs, sensory stimulation can also induce isolated SWs, most easily visible in sleep stage N2, called K-complexes. The 'K' is derived from the word 'knock', as the large slow wave was such a noticeable response to 'knocking on the sleeper's door' (Loomis et al., 1935a). K-complexes occur exclusively during NREM sleep, either spontaneously or evoked by any sensory stimulus (Cigánek, 1961; Goff et al., 1966), but most easily by auditory stimulation (Riedner et al., 2011). K-complexes have a refractory period of 10-15 seconds, in which a new K-complex cannot be elicited (Colrain, 2005). The function of K-complexes has been debated for decades as it seems to mark responsiveness to the environment as well as sensory gating. In recent years, a dual function has been proposed that underpins a self-inhibitory function (Halász, 2016). Evoked K-complexes start with an initial modality-dependent response (P200) in distinct cortical areas that is followed by a large downstate (N500) and terminates with a large up state again (P900) (Laurino et al., 2014; Riedner et al., 2011). In a self-inhibitory scenario, a stimulus of any modality would trigger a subsequent global silencing, largest in prefrontal areas, that interrupts cortical propagation and processing of the signal and therefore protects sleep (Fig. 1.4). Indeed, evoked activity resulting in a P200 response that is not followed by a large downstate is associated with further sensory processing, whilst the presence of a downstate is associated with further suppression of stimulation (Andrillon et al., 2016). Not only the function of K-complexes has been debated heavily, but also its relationship with SWs. One suggestion is that K-complexes are forerunners of SWs (Amzica & Steriade, 2002; De Gennaro et al., 2000). Indeed they are more easily elicited the closer they are to a transition from N2 to N3, which is rich in SWs (De Gennaro et al., 2000). Halász (2016) proposes a slightly more nuanced version in which K-complexes and SWs are part of a continuum of reactive sleep elements, where K-complexes are situated in between evoked potentials and SWs. In both views, K-complexes are isolated elements that resemble a slow wave with its bi-stable nature, which attempts to preserve sleep in response to a stimulus.

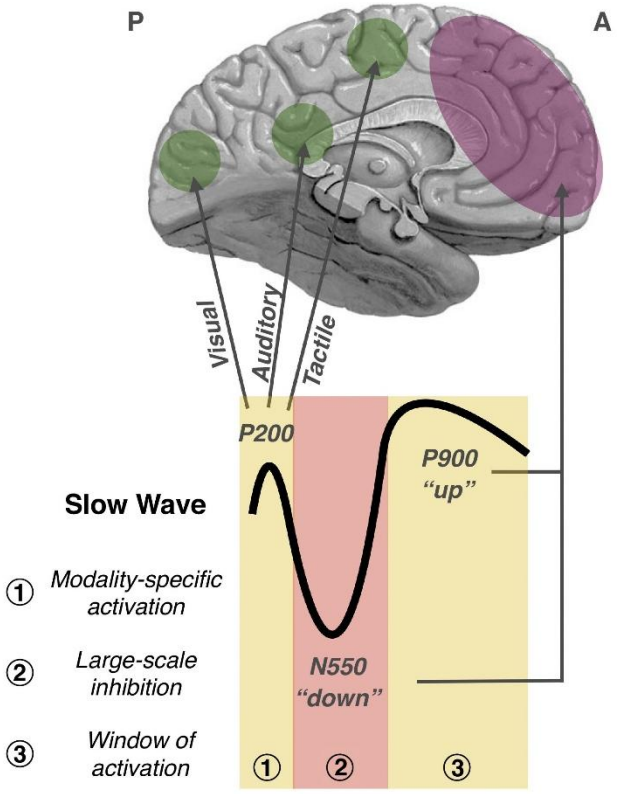

Figure 1.4 Evoked slow wave. P = Posterior; A = Anterior. Figure from Andrillon & Kouider (2020).

Sleep spindles. While many studies point at SWs as a potential mechanism that decouples the sleeper from its environment, SWs are not omnipresent throughout NREM sleep and can therefore not be the only mechanism of sensory disconnection. Another oscillation in NREM sleep has been associated with sensory disconnection, namely sleep spindles. Sleep spindles are short burst of activity in the sigma range (11 – 16 Hz) and a hallmark feature of sleep stage N2, although they are also present in N3 (See more detail in section 1.1.3).

The spindle gating hypothesis proposes that sleep spindles serve as protective elements, shielding the cortex from external input and thus promoting sleep maintenance. According to this theory, sleep spindle activity contributes to the effective gating of incoming sensory input, which ultimately decreases arousibilty. A growing body of literature supports this theory. An fMRI study shows that the signal transmission of simple tones is indeed limited during a spindle event, whilst being similar to responses during wakefulness when presented outside of a spindle event (Schabus et al., 2012). Not only is the flow of input interrupted, elevating sleep spindle power in mice through genetic overexpression of SK2-channels, that underlie spindle generation, is also accompanied by an elevation in arousal threshold (Wimmer et al., 2012). Even in humans, the pharmacological upregulation of sleep spindles raises the arousal threshold (Johnson et al., 1976). Additionally, individuals with more spindles per minute tend to be more resilient to waking up from external noise (Dang-Vu et al., 2010).

However, the spindle gating hypothesis is not supported by all findings. In rats, neuronal and local field potential (LFP) responses to a range of auditory stimuli, salient and non-salient, were similar in the presence or absence of a sleep spindle (Sela et al., 2016). In humans, neither cortical nor thalamic responses to nociceptive stimuli during sleep were affected by the presence of a sleep spindle (Claude et al., 2015), questioning whether sleep spindles facilitate sensory gating to any extent.

Another aspect which remains unclear is whether sleep spindles passively protect the brain from sensory interference or whether they are reactive elements and are upregulated in the face of noise. Research in favour of the latter suggests that sleep spindle density increases during a "stimulation period", when the participant's own name was spoken by a familiar or an unfamiliar voice (Ameen et al., 2022) and that intervals between spindles are shorter and spindle duration is longer in periods with stimulation (Sato et al., 2007). However, a study using transportation noise did not find an upregulation of sleep spindles and described a shortening of sleep spindles rather than lengthening (Rudzik et al., 2018). Similarly in rats, sleep spindles tend to be terminated prematurely by auditory input (Sela et al., 2016).

These seemingly contradictory results question whether and how sleep spindles actually gate sensory input. In their comprehensive review on sleep spindles, Fernandez & Lüthi (2020), suggest that the evoked responses seen during sleep spindles could indicate a cortical rather than thalamic gating mechanism of sleep spindles. Indeed, sleep spindles have a refractory period, 5-10 seconds in which a new sleep spindle cannot be initiated, which suggests there are lasting changes in the brain after a spindle event. So rather than individual sleep spindles gating incoming input, periods of increased sleep spindle activity might reflect a period of sensory disconnection. Indeed, humans and mice show infra-slow fluctuations during sleep around 50 seconds (Lázár et al., 2019), with phases more and less vulnerable to external perturbation (Lecci et al., 2017; Yüzgeç et al., 2018). Periods of less vulnerability are rich in sleep spindles compared to highly vulnerable periods.

Another question which remains is which features of sleep spindles contribute to effective gating, if they do so at all. A recent study in rats argues that not only the mere amount of sleep spindles matters, but the quality too, as the muscle activation in response to an auditory stimulus is lower in spindles with high - compared to low oscillatory strength (Blanco-Duque et al., 2024). This is interesting as sleep spindle characteristics such as amplitude and duration change with age (Crowley et al., 2018; Scholle et al., 2007), as will be addressed in more detail in section 1.2.3 and Chapter 4, and are often also affected in neurodevelopmental conditions (Herrera & Tarokh, 2024).

Although it is unclear if and how sleep spindles protect sleep, the majority of studies finds at least an association between sleep spindles, either quality or abundance, and responsiveness to the sensory environment.

Interestingly, sleep spindles originate in the TRN, a structure which is paramount in the processing of sensory input and part of the thalamo-cortical loop. More on the origins of sleep spindles will be discussed in section 1.1.3.

Local sleep and arousals. Lastly, an emerging theory on how a degree of vigilance is maintained during sleep is the phenomenon of local sleep and wake states. Sleep rhythms, such as slow waves, can appear locally and asynchronously (Siclari & Tononi, 2017). Also during wakefulness, local slow waves can intrude the awake brain activity, predicting lapses of inattention (Andrillon et al., 2021). One interesting study shows that during the first night in a novel environment the brain exhibits differences between hemispheres in vigilance states. One hemisphere will show deeper sleep than the other (Tamaki et al., 2016). Tamaki and colleagues describe this phenomenon as a 'night watch'. Interestingly, the more vigilant hemisphere showed not only enhanced neural responses to deviant sounds compared to the 'sleepy' hemisphere, but also more arousals when a stimulus was detected. This 'night watch' effect is even more pronounced in marine mammals that sleep with one hemisphere at a time (Dill et al., 1964). Furthermore, in response to stimulation, slow waves and sleep spindles can increase in one region, but decrease in another (Andrillon et al., 2016). Potentially local arousals during sleep can present regional windows to monitor the environment, whilst promoting sleep in another to prevent full blown awakenings.

In conclusion, while the flow of sensory input to the cortex is reduced during sleep, it is clear that some sensory input, depending on the saliency, can still reach the cortex during sleep. In NREM sleep, a *cortical gate*, alongside a partial *thalamic gate*, may explain selective processing of sensory input during sleep. Oscillations such as sleep spindles and slow waves may mediate the balance between sensory coupling and decoupling to the environment. Sleep spindles potentially reduce the flow of sensory input to the cortex, however, there is evidence supporting and opposing this theory. Slow waves, driven by underlying neural bi-stability, may establish the cortical gate by reducing the communication between cortical regions, explaining elevated arousal thresholds with deepening NREM sleep. Additionally, local sleep rhythms could explain selective processing of sensory input without necessarily arousing the sleeper. In this thesis, I do not go further into the local aspects of sleep. Instead, I focus on slow waves and sleep spindles, which are linked to sensory de-coupling during sleep and are altered in neurodevelopmental conditions, the latter is discussed further in Chapter 5.

Interestingly, both sleep spindles and slow waves have dual properties: They occur spontaneously, influencing incoming stimulation, and evoked, in response to stimulation. This underscores the influence of active strategies besides passive mechanisms that protect sleep from perturbation. Environmental and inter-individual differences may modulate both spontaneous and evoked brain activity. In Chapter 5, those dual properties are investigated in depth in individuals with a variety of sensory profiles.

In the next section of the introduction, I will go more in depth into the biological origins of these oscillations and discuss how they are generated as well as functions besides sensory gating. Understanding where SWs and sleep spindles come from is important to understand which factors may influence their spontaneous and evoked presentations. In Chapter 5, we look at whether spontaneous and/or evoked oscillations are altered depending on an infant's sensory profile.

1.1.2 Slow waves and K-complexes

How are slow waves and K-complexes generated?

Slow waves and K-complexes that are visible on the scalp EEG depict the synchronized bi-stable slow oscillation in neuronal populations. The features of cortical slow waves seen in the EEG signal depend on the size and efficiency of neuronal populations that exhibit the slow oscillation and the degree of synchrony between neurons. The *amplitude* and overall *slow wave activity* depend on the number of neurons that fire synchronously. The *steepness* of the slopes—both descending and ascending—shows how quickly and synchronously neighbouring neurons can switch between the ON and OFF states. The steepness indicates the efficiency of the transition between activation and silence. Lastly, the *prevalence* of slow waves reflects the tendency for neurons to enter the down state.

It was originally thought that slow waves originated in the neocortex, as the slow oscillation could emerge in isolated neocortical slices (Sanchez-Vives & McCormick, 2000), but did not appear in the thalamus of de-corticated animals (Timofeev & Steriade, 1996). However, subsequent studies showed that activity in the thalamus precedes cortical slow waves (David et al., 2013) and that cortical slow waves are interrupted when the thalamus is functionally disconnected, although only temporarily (Lemieux et al., 2014). In conclusion, an intricate interplay between thalamus and neocortex is likely needed to initiate the slow waves seen in vivo. Single neurons can produce a slow wave rhythm, but the large synchronization and almost exact simultaneous start of silent states in neurons far apart (12 mm) implies that some sort of central coordination must be present (Volgushev et al., 2006). However, slow waves are not perfectly synchronized across the whole cortex (Amzica & Steriade, 1995). Instead, slow waves propagate through the cortex, with a speed of up to once per second, usually in an anteroposterior direction (Massimini et al., 2004). This suggests slow waves are regulated centrally

likely by subcortical structures and propagated cortically. It is thought that slow waves and K-complexes have similar origins, both underpinned by the bistable dynamics of the brain, but it is still unclear what triggers one or the other (Bellesi et al., 2014).

Homeostatic influences on SWs and K-complexes

Both night sleep and naps are believed to be regulated by circadian rhythms and homeostatic sleep drive (Borbély, 1982). Homeostatic sleep pressure builds up during wakefulness and dissipates during sleep. This sleep pressure is what makes us feel tired after a long, exhausting day even if it is still light outside. SWA is often used as a proxy for homeostatic sleep pressure, or simply referred to as 'sleep need'. After sleep deprivation, SWA is increased and SWA dissipates over the course of the night (Dijk et al., 1987, 1990; Esser et al., 2007; Pappenheimer et al., 1975). Also spontaneous and evoked K-complex occurrence is higher in a night after sleep deprivation and their incidence decreases over the course of the night (Nicholas et al., 2002; Rajna et al., 1983). So, the occurrence of spontaneous and evoked SWs and K-complexes is partly driven by the needs of the sleeper at that moment, with more SWs and K-complexes when high sleep pressure is high.

Cellular mechanisms behind slow wave dynamics

Although SWA appears to reflect homeostatic pressure, there is still debate about the mechanisms behind the changes in SWA. Two theories explain the mechanism behind the increase in SWA after prolonged wakefulness and the following decrease during sleep. One hypothesis suggests that neurons get fatigued from firing (Vyazovskiy & Harris, 2013), for example due to depletion of energy resources, such as glycogen (Dalsgaard & Secher, 2007) or calcium (O'Donovan & Rinzel, 1997). To recover from this fatigue, neurons need extended periods of inactivity, leading to the synchronous OFF periods during SW sleep. Another, more widely accepted theory is the synaptic homeostasis hypothesis (SHY), which states that SWs are not a response to fatigued neurons per se, but that learning in particular drives the increase in SWA (Tononi & Cirelli, 2006). Wake experiences are encoded, primarily through input-dependent long-term potentiation (LTP), which results in an overall increase in synaptic strength during wake. Without synaptic downscaling, which reduces synaptic strength, synapses would be saturated and that would leave neurons unable to continue learning. Sleep, and in particular SWs, rebalance the system by downscaling the synapses, which allows for new encoding during wakefulness the next day and also contribute to selective pruning and forgetting (see Fig. 1.5). According to the SHY, the increase in SWA after periods of wakefulness is caused by an increase in neuronal synchrony through stronger synaptic coupling, the longer the wake period or the more learning occurs, the stronger the synaptic coupling. Accumulating evidence favours the synaptic homeostasis hypothesis over the 'neuronal fatigue' hypothesis. For example, Rodriguez et al. (2016)

show that SWA increases in mice after exploratory wakefulness, which is assumed to be accompanied by higher synaptic plasticity, but not after neuronal activation by optogenetic stimulation, which 'fatigues' the neurons without leading to learning. Moreover, in humans, local increases in SWA are seen in brain regions involved in a learning task during prior wake (Huber et al., 2007), suggesting again a special role of pre-sleep learning in subsequent SW production. In return, the decrease in SWA over the course of sleep, reflects the weakening of synapses and a reduction in the strength of corticocortical connections, which is essential for facilitating the encoding of new memories the next day.

In summary, slow waves, generated through a complex interplay between the neocortex and thalamus, reflect the synchronized bi-stable slow oscillation in neuronal populations. The dynamics of slow waves are closely linked to homeostatic sleep pressure, increasing after prolonged wakefulness and gradually decreasing as sleep progresses. The synaptic homeostasis hypothesis offers a compelling explanation for these changes, suggesting that slow waves help to restore synaptic balance after wakefulness by downscaling synaptic strength. This process preserves the brain's capacity for learning.

Therefore what happens before sleep partly determines how connected or disconnected a sleeper is to the environment the next night. Sleep is prioritized over vigilance when synaptic homeostasis needs to be rebalanced. Interestingly, SWA does not only change over the course of the night, but it also changes across development, with high SWA during infancy and childhood. More on that will be discussed in section 1.2.2. of this chapter; but first I discuss the generation and function of sleep spindles.

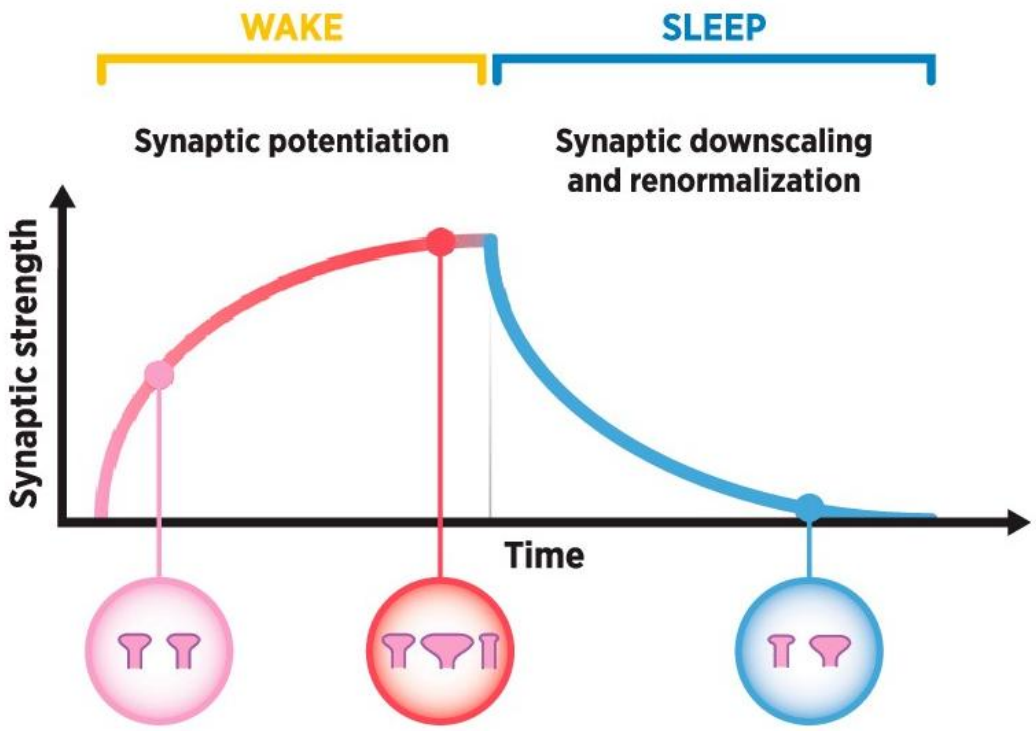

Figure 1.5 Synaptic Homeostasis Hypothesis (SHY). Figure adapted from Rantamäki & Kohtala (2020).

1.1.3 Sleep spindles

Sleep spindles are named after their resemblance to a spindle used for wool spinning (Loomis et al., 1935b). Loomis gave both sleep spindles and K-complexes their names and left a legacy of creative naming behind. Sleep spindles are burst of activity around 11-16 Hz that last more than 0.5 s, with a characteristic 'waxing' and 'waning' shape (see Fig. 1.6A)(Iber et al., 2007).

Sleep spindles are most commonly measured as discrete events or as power in the sigma frequency band. Sigma power represents the squared amplitudes of oscillations in the sigma range (somewhere in between 7-16 Hz) averaged over a time period (Fernandez & Lüthi, 2020). This period is often sleep stage N2, but can also include N3. When the power spectrum is plotted during N2, usually a prominent peak is visible in the sigma range (Fig. 1.6B). The shape of that peak and its topographical distribution is remarkably unique to an individual and has been called 'a fingerprint of sleep' (De Gennaro et al., 2005). Alternatively, sleep spindles can be measured as discrete events, detected visually or automatically (See more detail on this in Chapter 4). From these distinct events a number of features can be extracted, such as the sleep spindle density, average time interval between sleep spindles, amplitude or power, frequency (number of cycles per min) and duration (See fig. 1.6A). In humans - but not in all animals (e.g. mice (D. Kim et al., 2015), sheep (W. T. Schneider et al., 2020) and cats (Iotchev & Kubinyi, 2021)) - sleep spindles can be subdivided into slow (<13 Hz) and fast (>13 Hz) sleep

spindles, that are topographically separated. Slow spindle activity occurs predominantly over frontal channels whilst fast spindle activity is highest over central channels (Gibbs & Gibbs, 1950).

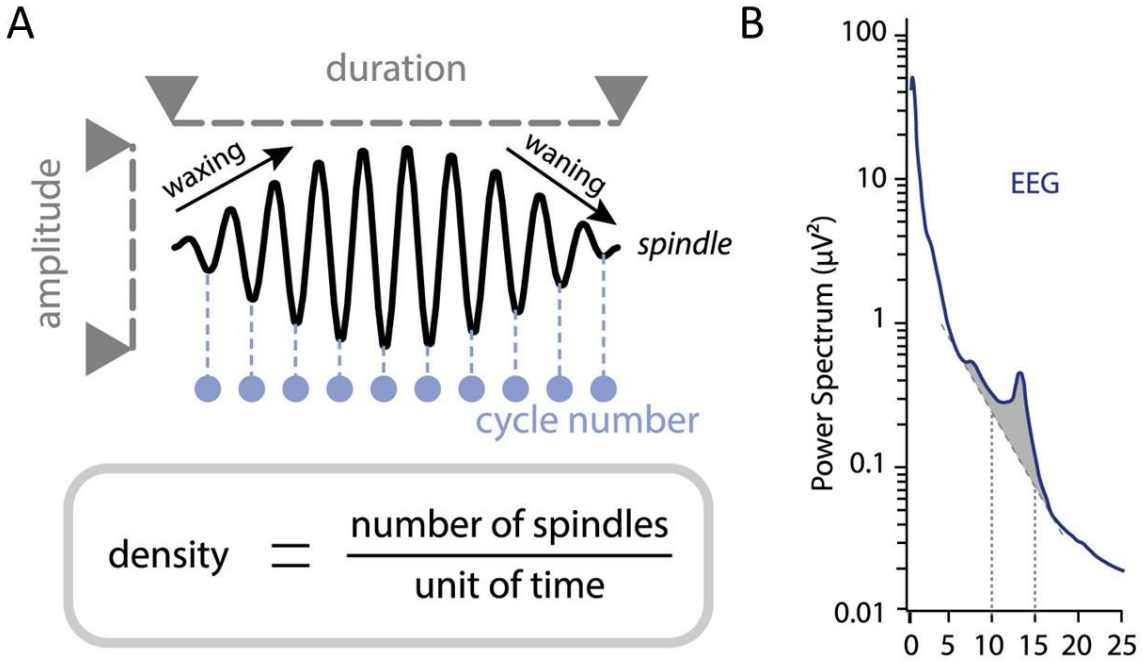

Figure 1.6 ***A.*** *Sleep spindle features.* ***B.*** *Power spectrum in N2. Adapted from Fernandez & Lüthi (2020).*

How are sleep spindles generated?

The sleep spindles that we observe on scalp EEG recordings are only a surface manifestation of oscillations generated by a deeper structure situated in the thalamus, the thalamic reticular nucleus (TRN). A structure which was described earlier in relation to sensory processing (see Fig. 1.1). The TRN is a thin sheet of inhibitory neurons surrounding the dorsal thalamus that is the most prominent source of Gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the brain (Crabtree, 1999) and has a purely modulatory function (Pinault, 2004). TRN neurons fire in a 'tonic'- or 'burst'- mode, depending on vigilance state. During wakefulness, TRN neurons are in the tonic mode and signals from the ascending pathways passing through the thalamus to the cortex are left relatively unaltered. However, in the burst-mode during sleep, signal transmission via thalamocortical relay is altered, though not completely extinguished (Mukherjee & Kaplan, 1995). In burst mode a higher signal-to-noise ratio facilitates signal transmission of relative changes in input rather than the reliable, linear signal transmission that occurs in the tonic mode during wakefulness. A unique feature of this system is that novel stimuli can trigger a switch from burst to tonic mode, therefore increasing reliable information transmission in response to salient stimuli (Guillery et al., 1998).

The importance of the TRN for the generation of spindles was first discovered by Steriade et al. (1985). They demonstrated in cats in vivo that the isolated TRN, deprived from major cortical and thalamic

input sources, could still produce spindle oscillations. Thalamic nuclei disconnected from the TRN on the other hand lost the ability to produce spindle rhythms (Steriade et al., 1985).

During sleep, when TRN neurons switch to the burst mode, TRN neurons cause an exceptionally strong and synchronous inhibition of thalamo-cortical neurons. After repeated inhibitions, thalamo-cortical neurons will exhibit excitatory rebound bursts in response. Thalamo-cortical neurons have excitatory projections to the cortex and collaterals to the TRN. These are open loop projections, meaning that they will not project to the same TRN neurons which caused the excitation in the first place, but instead project to adjacent TRN neurons. The result is a lateral spread of the TRN and thalamo-cortical bursts and eventually a synchronized spread of spindle activity. After repetitive bursting, thalamocortical neurons enter a afterdepolarized state, which prevents further activity (Bal & McCormick, 1996). The combination of thalamic, cortical and brainstem activity likely causes the termination of a sleep spindle and the following refractory period, that lasts 5-10 seconds, before a new sleep spindle can be initiated.

Due to the importance of the TRN for state-dependent signal transmission, as well as its importance for the generation of sleep spindles, TRN impairment has been suggested as a factor driving the co-occurrence of sleep and sensory processing in neurodevelopmental conditions (Krol et al., 2018). More on potential mechanisms that link sleep and sensory processing will be discussed in 1.3.2.

Sleep spindle functions

Besides a protective function of sleep spindles, gating sensory input, as described above, sleep spindles have also been implicated in synaptic plasticity and memory.

The role of sleep spindles in memory consolidation is perhaps its most studied aspect (See review (Peyrache & Seibt, 2020)). In humans, pre-sleep learning is followed by an increase in sleep spindle amplitude and density, particularity in context of declarative or procedural memory tasks (Fogel & Smith, 2006; Schabus et al., 2004), but not for episodic memory (Ackermann et al., 2015). Enhancing sleep spindles through transcranial direct or alternating current stimulation in humans improves declarative memory (L. Marshall et al., 2006) and motor consolidation (Lustenberger et al., 2016). However, not just the amount or strength of sleep spindles is linked to learning, but also the timing of sleep spindles in relation to other oscillations. The 'active systems consolidation' theory describes that memories are consolidated by reactivation of memory traces during SWS (Born & Wilhelm, 2012). However, some memories traces are strengthened while others are weakened when transferred from temporary storage in the hippocampus to long-term storage in the neocortex. According to this theory, the integration of memories in the long-term storage is facilitated by the synchronization of neocortical slow oscillations, thalamo-cortical sleep spindles and hippocampal sharp wave ripples.

Indeed, sleep spindles that are in phase with cortical slow waves up states enhance memory consolidation more than those that are out of phase (Latchoumane et al., 2017).

Both sleep spindles and SWs play a key role in the consolidation of memories (Rasch & Born, 2013). It is thought that memory replay, a key part of the successful consolidation of memories, happens during NREM sleep. When memory traces are replayed, or reactivated, they are temporarily vulnerable to external perturbation and susceptible to modification by other input. Thus, the ideal state for memory consolidation is therefore an 'offline' state, when the brain can turn inwards without interruption from the outside world. That SWs and sleep spindles are implicated in both sensory gating and memory consolidation is therefore perhaps not surprising, as minimal interference is optimal for reliable consolidation. One possibility is that these rhythms just reflect a period of sensory disconnection, however, the research outlined above in section 1.1.1. suggests an active role for SWs and sleep spindles in decoupling the sleeper from their environment, whilst still maintaining a degree of vigilance.

Most of the studies mentioned above are based on adult data in humans or rodents. In the next section, I will give an overview of sleep in infancy and discuss the development of sleep spindles and slow waves.

1.2 Sleep in infancy

Across the lifespan, sleep patterns and sleep architecture change significantly (Skeldon et al., 2016). For example, adolescents start going to bed later and wake up late, while elderly tend to rise early, under influence of changing circadian rhythms. Sleep need also varies across the lifespan, with infants and children needing substantially more sleep than adults. The increased sleep need during early development is believed to support the high rates of learning and neuroplasticity during that time (Frank et al., 2001; Frank & Heller, 2019).

Sleep is a multidimensional term, that covers behavioural, physiological and neural levels. Different aspects of sleep broadly fall into two categories: sleep macro-architecture and sleep micro-architecture. In Box 2, I provide examples of sleep macro- and micro-architecture aspects and through which methods these various aspects can be assessed in infants. Below, I will discuss changes in sleep macro- and micro-architecture across infancy, which maps onto the age range in Chapter 2 and 3 (5-14 months). I will then delve deeper into SW and sleep spindle development in the first year of life to provide a framework for assessing how 'mature' these oscillations are between 8 and 11 months, the age range of Chapter 4 and 5. Lastly, I discuss the link between these changes and brain maturation to understand why individual trajectories of sleep macro- and micro-architecture may differ.

Box 2. Measuring sleep in infants

Table 1.2 Examples of sleep macro- and micro-architecture variables of sleep. This list provides a few examples and is not exhaustive.

Sleep macro-architecture			**Sleep micro-architecture**	
Quantity and Quality	*Circadian factors*	*Sleep stage distribution*	*Phasic events*	*Spectral components*
▪ Sleep duration (night and/or daytime) ▪ Sleep efficiency ▪ Frequency of awakenings ▪ Wake after sleep onset (WASO) ▪ Sleep onset latency ▪ …	▪ Timing of sleep onset ▪ Morning rise time ▪ Distribution of naps ▪ …	▪ Time in each sleep stage (N1, N2, N3 and REM) ▪ Percentage in each sleep stage ▪ …	▪ Sleep spindles ▪ K-complexes ▪ Slow waves ▪ Micro-arousals ▪ Rapid Eye Movements ▪ …	▪ Any frequency band

Sleep measures are typically divided into two categories: sleep macro- and micro-architecture. Sleep macro-architecture refers to the larger structural components of sleep. These can be further subdivided into sleep quantity and quality, circadian factors or sleep schedule and sleep stages. Sleep micro-architecture refers to more granular features of sleep at the level of brain activity. In table 1 examples of each category are given. However, it should be noted that some variables may overlap across categories. For example, the percentage of time spent in N3, is closely related to sleep quality.

Infant sleep can be assessed using a variety of methods, depending on the research objectives and available resources. These methods include polysomnography, videosomnography, actigraphy, and subjective reports, like questionnaires and sleep diaries (Sadeh, 2015). While polysomnography is considered the gold standard in sleep research, it presents unique challenges in the context of infant sleep, such as safety concerns and the difficulties of EEG setup (Sadeh, 2015). Subjective reports and actigraphy are easier and cheaper methods to assess sleep, but are not always reliable . Moreover, polysomnography is the only method that provides reliable estimates of sleep stages and measures of brain activity, such as sleep spindles and slow waves. See table 2 for a summary of which methods are able to assess different aspects of sleep.

Table 1.1 Sleep measurement methods.

Type of measurement	**Sleep macro-architecture**			**Sleep micro-architecture**	
	Quantity and Quality	*Circadian factors*	*Sleep stage distribution*	*Phasic events*	*Spectral components*
Subjective reports	X	X			
Actigraphy	X	X			
Videosomnography	X	X			
Polysomnography	X	X	X	X	X

1.2.1 Changes in sleep macro- and micro-architecture in infancy

Human newborns spend the majority of the day asleep, transitioning between wake and sleep irregularly multiple times a day, a pattern known as polyphasic sleep. Around 4 months of age, infants start to develop a day-night or circadian rhythm, mostly sleeping at night and being awake during the day (Iglowstein et al., 2003). By around 9 months, infant sleep becomes triphasic, consisting of one big bout of sleep at night and two naps during the day (Weissbluth, 1995). Between the first and second year, infant sleep becomes diphasic when infants drop from two to one nap a day. In toddlerhood, sleep patterns become similar to adulthood, when toddlers transition to monophasic sleep (Staton et al., 2020).

Not only the amount and pattern of sleep differ greatly from adulthood, sleep stage distributions are vastly different in infancy as well (Lenehan et al., 2023). In sleep research, the identification of sleep stages relies on physiological signals from polysomnography, which includes EEG, electromyography (EMG), electrooculography (EOG) and sometimes heart rate and breathing measures. Visual identification of sleep stages (See box 1) is ideally compared between two expert sleep scorers and is considered the gold standard. However, in recent years, automated methods have become popular due to the time-consuming nature of manual sleep scoring (Fiorillo et al., 2019). In neonates, EEG activity looks so distinct from adults that sleep cannot be classified into adult-like sleep stages. Instead sleep is divided into quiet sleep (QS), active sleep (AS) and indeterminate sleep (Grigg-Damberger Madeleine, 2016). From 3 months onwards, adult-like sleep features start to appear that facilitate the division into sleep stages N1, N2, N3 and REM (Grigg-Damberger Madeleine et al., 2007). However, sleep EEG features, such as sleep spindles and slow waves undergo large developmental changes even after they start to appear in the EEG signal (See more info in 1.2.2 and 1.2.3). Furthermore, the proportion of REM/NREM sleep changes drastically across the lifespan. REM sleep dominates in the first months of life, but gradually NREM sleep becomes more prominent reaching adults levels at the end of the first year of life (Jenni et al., 2004).

Individual sleep trajectories can vary greatly from the average, influenced by a complex interplay of factors. Biological and genetic factors, such as melatonin production (Touchette et al., 2013) and sleep practices, such as settle methods (Henderson et al., 2020), bedsharing and breastfeeding (Hysing et al., 2014), all contribute to how an infant's sleep develops. Additionally, changes in sleep patterns do not always occur linearly and sudden changes may be related to other developmental milestones (Atun-Einy & Scher, 2016). See figure 1.7 for a summary of the changes in sleep in the first year of life.

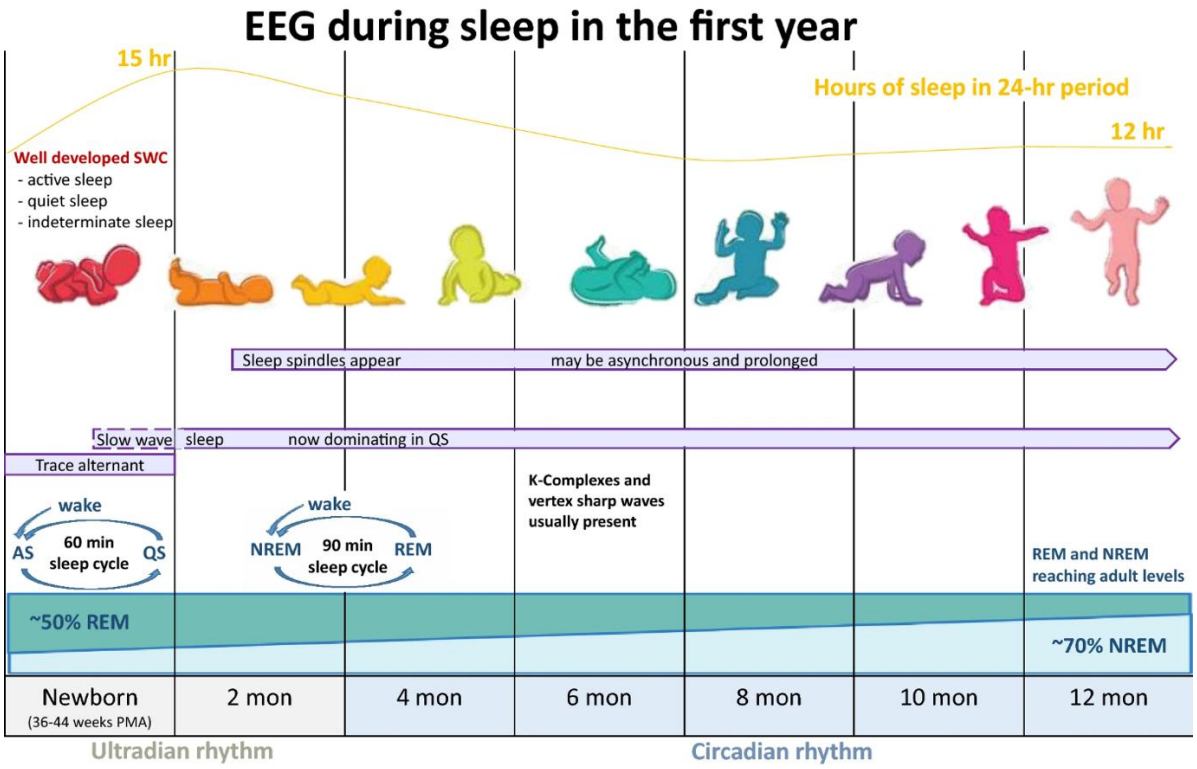

Figure 1.7 Development of sleep and its EEG features in the first year of life. Figure from Lenehan et al. (2023).

1.2.2 Development of slow waves and K-complexes

Slow waves

Already in neonates, some form of slow wave activity is present, but defined and distinct slow waves or trains of slow waves are not visible in the EEG yet (Ellingson & Peters, 1980). These only appear gradually within the first six weeks after birth (Dan & Boyd, 2006). From 2 months, slow waves start to show homeostatic properties, with a decrease in amplitude and slope steepness over the night (Fattinger et al., 2014; Jenni et al., 2004). Between two to nine months slow waves continue to evolve, showing increasing amplitudes and steeper slopes (Fattinger et al., 2014). Increasing rates of synaptogenesis, which improves the efficiency of neurons transitioning between up- and down states, may underlie the development of steeper slopes and higher amplitudes of SWs. Additionally, the topography of slow waves changes across development, with higher SWA in occipital regions during infancy and early childhood (Novelli et al., 2016; Sokoloff et al., 2021). Over time, SWA maxima shifts in a posterior-to-anterior direction throughout childhood and adolescence, until maxima occur frontally (Kurth et al., 2010).

K-complexes

The literature on K-complexes in infancy is surprisingly limited, which may be due to the difficulty in detecting them. A K-complex is defined as an isolated event that stands out from the EEG background signal (see Fig. 1.8A. for a typical K-complex in adults). However, due to the high amplitude, low

frequency background EEG activity in infancy, K-complexes are not as easily identified as in adults. K-complexes are thought to appear around 5- to 6-months-of-age (Lenehan et al., 2023). Metcalf et. al (1971) suggest that K-complexes might be present earlier, but are not discernible from the background EEG. According to them, adult-like K-complexes are only visible from 7 years onwards. In a longitudinal study, Verma & Baisakhiya (2021) do not find any K-complexes in newborns and 3-month-olds. However, by six months-of-age, the majority of infants – around 80% - have visible K-complexes, which increased to 90% at 9 months and 95% at 12 months. In addition, the shape of K-complexes evolves from a blunt shape at 6 and 9 months to a sharper shape - similar to adults - at 12 months. The studies by Metcalf (1971) and Verma & Baisakhiya (2021) focus on the development of spontaneous K-complexes. There is some evidence for the presence of evoked K-complexes in 3- to -5-month-old infants (King et al., 2018). In this study, K-complexes are averaged across trials, but no information is provided on how many K-complexes were detected per infant. However, the study shows clear K-complex responses to auditory stimulation early in infancy (see Fig. 1.8B).

In conclusion, K-complexes start to appear in the EEG signal between 3 and 6 months-of-age, but the presence or visibility is highly variable between individual infants. In Chapter 4, I discuss the visibility and development of K-complexes in more detail and the implications for detection in infancy.

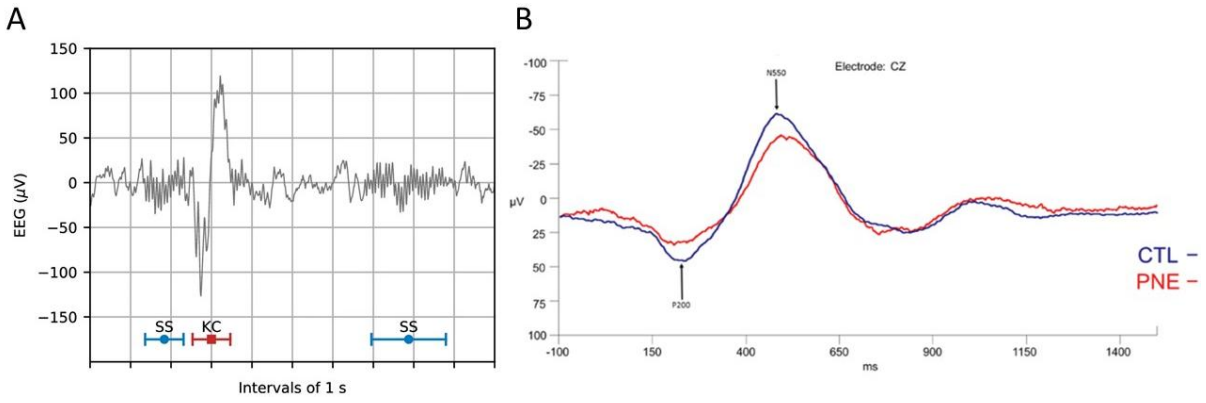

Figure 1.8 Examples of K-complexes. A. Typical K-complex in adults. KC: K-complex; SS: Sleep Spindle. Figure from Tapia-Rivas et al. (2024) B. Averaged evoked K-complexes from a study in 3-5 month-old infants. Notice that the Y-axis is plotting negative voltages upward, opposite to part A. CTL: Controls, PNE : Infants exposed to nicotine prenatally. Figure adapted from King et al. (2018).

1.2.3 Development of sleep spindles

As discussed in section 1.1.3, the initiation, synchronization and termination of sleep spindles rely on a complex interplay between thalamocortical neurons and TRN neurons. The maturation of those neurons and their connections are essential for the generation of a sleep spindle. Research in animals shows that thalamocortical and TRN neurons undergo rapid maturational changes during the postnatal period (Murata & Colonnese, 2019; Pirchio et al., 1997; Warren & Jones, 1997).

True sleep spindles, as seen in adults, only start to appear in the EEG signal of 6-week to 3-month-old human infants (Ellingson & Peters, 1980; Louis et al., 1992). In rodents, the emergence of sleep spindles coincides with maturational trajectory of the thalamic circuit (Jouvet-Mounier et al., 1969), confirming the need for developed thalamic structures to produce sleep spindles. Sleep spindles are therefore also used as a marker for thalamocortical connectivity (Jaramillo et al., 2023). In adults, sleep spindles are typically symmetric, occurring simultaneously in both hemispheres. They predominantly appear in central and frontal EEG channels and can be categorized into fast and slow spindles (see 1.1.3). However, when sleep spindles first emerge in infants, they are often asymmetric (Ellingson, 1982), with only one sigma peak visible on the spectrogram, around 13 Hz (Jenni et al., 2004), rather than two distinct peaks seen in adults. It is only after 12 months, between the 1st and 2nd years of life, that two distinct sigma peaks start to emerge in frontal and central channels (Kwon et al., 2023). Additionally, the amplitude and duration of sleep spindles shows clear differences in the first year of life compared to adulthood. In the first few months when sleep spindles appear, they tend to have a smaller amplitude and have a longer duration, around 1-4 seconds, compared to 1-2 seconds in adults (Fernandez & Lüthi, 2020; Ventura et al., 2022). The development of different sleep spindle characteristics across the lifespan are summarized in figure 1.9.

In summary, sleep spindles emerge in the first months of life, but undergo maturational changes that are likely linked to the maturational stage of the thalamocortical circuit. Early sleep spindles are similar to adult ones, but show distinct differences in features such as sleep spindle duration, frequency and amplitude. This has implications for the detection of spindle events, which will be discussed in Chapter 4.

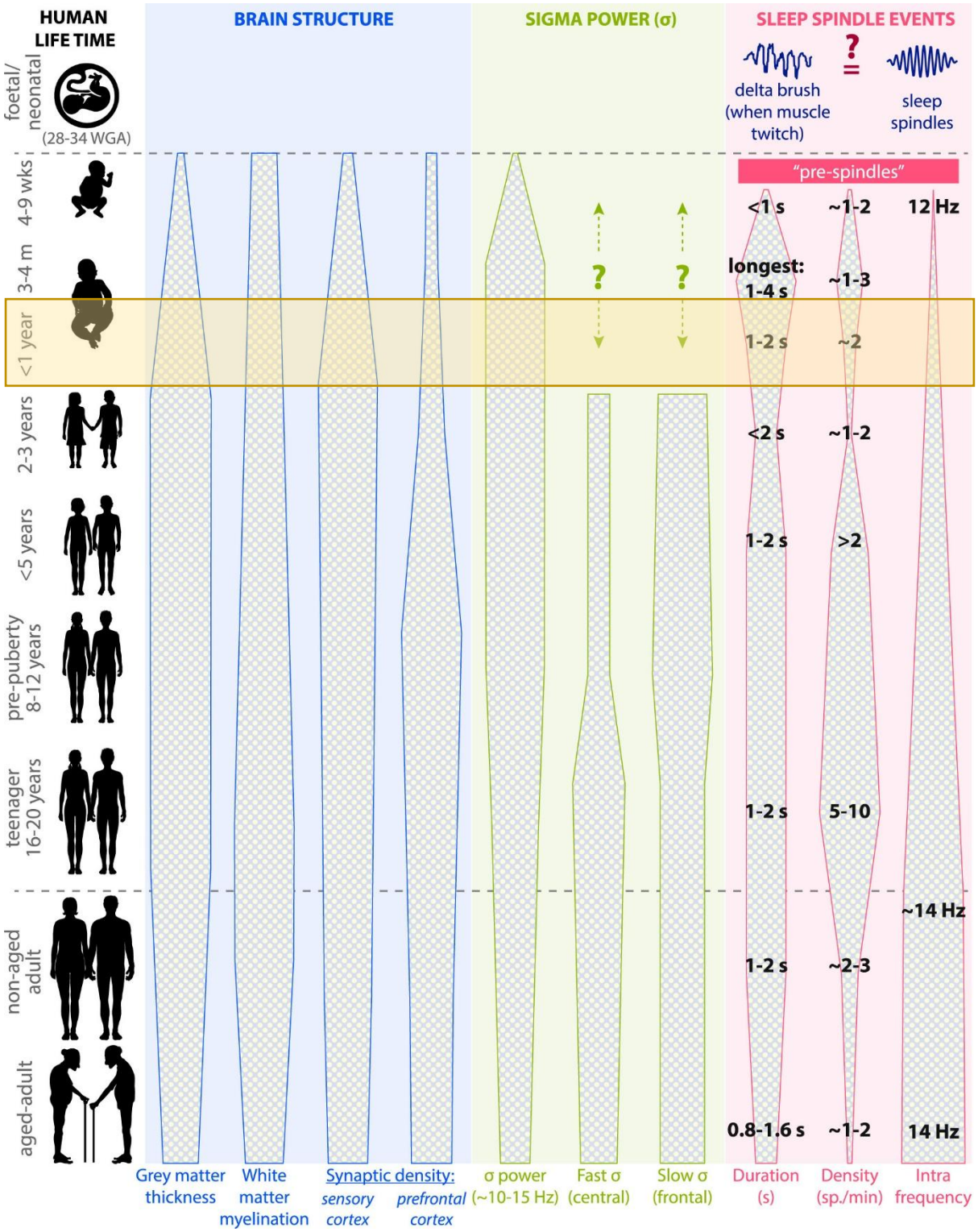

Figure 1.9 The development of sleep spindle features and brain structures across the lifespan. The intra-frequency is the number of oscillations per sleep spindle, referred to as just 'frequency' in the text. The approximate time window that will be investigated in this thesis is highlighted in yellow. Figure from Fernandez and Lüthi (2020).

1.2.4 Early sleep and brain development

The substantial changes in sleep patterns, architecture and oscillations that occur during development likely mirror brain maturation. For example, sleep-wake rhythms can only occur once connections

between circadian clock regions and behavioural output neurons are formed (Poe et al., 2023). Before those connections are made, it is anatomically impossible for infants to exhibit circadian behaviours. The emergence of circadian rhythms therefore reflects the maturation of long-range connections in the brain. Also transitions in sleep patterns have been suggested to reflect changes in brain maturation. Spencer & Riggins (2022) propose that the amount of naps a child takes, may reflect the maturity of the hippocampus. In theory, an immature hippocampus is less efficient and cannot store as many short-term memories as a mature hippocampus. Therefore an immature hippocampus needs to "offload" memories more often in the long-term storage, a process that is sleep-dependent (See 'active systems consolidation' theory in 1.1.3). Spencer & Riggins's theory is supported by a study showing that toddlers that nap habitually have greater memory loss when deprived of a midday nap than non-habitual nappers (Kurdziel et al., 2013). Furthermore, nappers tend to have larger hippocampal volumes than non-nappers (Riggins & Spencer, 2020). According to the authors, a larger volume may suggest that less synaptic pruning has occurred, a process linked to structural maturation.

Interestingly, circadian rhythms and as a result longer and deeper sleep at night, are essential to unlock more sophisticated learning. In an elegant study using fruit flies, Poe et al. (2023) show that deep sleep is needed for improvement on a long-term memory task, but not a short-term memory task. This in turn suggests that sleep not only mirrors brain development, but drives it as well.

As early as 1966, Roffwarg proposed that early sleep, particularly REM sleep, plays a pivotal role in neurodevelopment. This theory was based on the observation that sleep is abundant in early life, with a notably high proportion of REM sleep. The fact that this pattern is conserved across species further underscores the importance of early sleep in development (Jouvet-Mounier et al., 1969). Since Roffwarg's initial proposal, the study of sleep ontogenesis and its relationship to brain maturation has been a growing area of research, gaining more traction in recent years, as evidenced by the accumulation of reviews on this topic recently (de Groot et al., 2024; Gorgoni et al., 2020; Knoop et al., 2021; Kurth et al., 2015; Lokhandwala & Spencer, 2022; Riggins et al., 2024).

On a neural level, major changes happen across development. Initial rapid growth in synapses and connections between neurons is followed by synaptic pruning, which improves the efficiency of the brain by refining and specializing neural networks. Synaptic density follows an inverted U-shaped trajectory from birth to adulthood with a peak during childhood, when the brain has more neural connections than during adulthood (Rakic et al., 1986). While Roffwag saw a major role for REM sleep, more recently it is proposed that both REM - and NREM sleep have distinct functions that contribute to neurodevelopment (Knoop et al., 2021). REM sleep is believed to contribute to the expansion of neural networks, by providing endogenous activity, while NREM sleep optimises these networks

through synaptic downscaling and pruning. This theory may explain the shift in sleep stage proportions across development, with a larger proportion of REM sleep in infancy and a predominance of SWS during childhood. That SWS may be involved in synaptic pruning is supported by the fact that SWA maxima travel in an posterior-to-anterior direction during development paralleled by cortical maturation (Kurth et al., 2010; Shaw et al., 2008). These results *an sich* do not provide enough evidence for a causal relationship from SWs to cortical pruning, but instead could indicate that SWA is a proxy for cortical matureness.

In humans, it is challenging to provide evidence for a causal relationship between early sleep and brain development. However, animal studies can provide some insight in the role of early sleep by disrupting sleep in a specific time window early in life and measuring neural and behavioural outcomes later in life. An experimental study in prairie voles shows that early life sleep disruption – decreased REM sleep and more fragmentation of NREM sleep – results in increased dendritic spine density, spine immaturity and altered glutamatergic neurotransmission in adulthood (Jones et al., 2021). At a behavioural level, these prairie voles show impaired social behaviour (Jones et al., 2019) and less cognitive flexibility (Jones et al., 2021) later in life. Similarly, induced sleep loss in young fruit flies results in deficits in courtship brain structures and behaviour (Kayser et al., 2014). These studies confirm that early sleep has lasting impacts on brain development and behaviour.

Using a longitudinal design, a few studies in human infants show that early sleep predicts later structural brain features as well as behaviour. For instance, the trajectories of sleep duration in the first year of life, assessed with caregiver reports, predict white matter volume at 12 months of age (Pittner et al., 2023). Infants that showed less of a decrease in sleep duration had greater white matter volumes. White matter reflects the myelination of axon bundles and is important to increase the efficiency of signal transmission in the brain (Paus et al., 2001). The authors interpreted the results as meaning that more sleep is needed for white matter maturation. Besides structural features, behavioural outcomes are also be predicted by early sleep features. Sleep spindle density at 6 months, but not SWA, SW slope or sleep spindle/SW coupling, predicts overall developmental status at 12 months and motor development at 12 and 24 months (Jaramillo et al., 2023).

In conclusion, sleep is a dynamic process that changes across development. Changes are especially large in the first year of life, likely contributing to *and* reflecting brain maturation. The features that are associated with sensory processing during sleep in adulthood, slow waves, K-complexes and sleep spindles, are still developing in infancy and early childhood, which raises questions about their functionality in terms of sensory gating at that time in life.

So far, I have discussed sleep and sensory processing during sleep in typical populations. In the next section, I explore whether sleep is affected in individuals who show heightened awareness and annoyance to sensory input during wakefulness. I therefore turn to sleep and sensory processing in autism, a condition in which sensory processing differences and sleep difficulties are common.

1.3 Sensory processing differences and sleep

1.3.1 Autism

Autism spectrum disorder (ASD), or simply autism, is defined in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) as a condition characterised by two core domains: 1. persistent deficits in social communication and social interaction and 2. restricted, repetitive behaviours, interests or activities. The DSM- 5 highlights that these symptoms must be present in the early developmental period, but recognises that they may only become fully evident when social demands surpass an individual's social capacities or that these symptoms may be masked later in life. The DSM-5 also emphasizes that these symptoms should not be better explained by intellectual disability or developmental delay. In addition, the symptoms a person exhibits must cause significant difficulties in daily functioning (American Psychiatric Association, 2013).

The diagnosis of autism relies on behavioural signs and autism can therefore usually only be diagnosed reliably by the age of three (Steiner et al., 2012). However, symptoms of autism often emerge much earlier. Studying autism before a formal diagnosis is important for early detection of autism and to develop potential early interventions, as well as to contribute to our understanding of the aetiology of autism (Gliga et al., 2014). To do so, we can use prospective studies of infants at elevated likelihood of developing autism (EL), who have an older autistic sibling diagnosed. By the age of three, nearly half of EL-infants will either be diagnosed with autism themselves, approximately 20%, or show subclinical symptoms, around 10-20% (Messinger et al., 2013; Ozonoff et al., 2011, 2024).

The earliest measures that predict diagnostic outcome are sensory and motor behaviours, as early as 6 months (Estes et al., 2015; Sacrey et al., 2015), while other symptoms such as social communication differences do not predict diagnostic outcome until after 12 months (Estes et al., 2015; Sacrey et al., 2015).

1.3.1.1. Sensory processing differences in autism

In the earlier editions of the DSM, sensory processing differences were not included as a core diagnostic symptom (Grapel et al., 2015), despite autistic individuals consistently highlighting these experiences in their personal accounts of autism (Chamak et al., 2008; Grandin, 2009). Moreover,

these sensory differences were already acknowledged by Leo Kanner in his initial observations of autism (Kanner, 1943). In the fifth edition of the DSM, sensory processing differences, both hyper- and hypo-reactivity to sensory input, were finally included as a core diagnostic feature of autism under the category of repetitive and restrictive behaviours. Indeed, sensory differences are prevalent in the majority of autistic people, estimated in up to 90% of autistic individuals (Ben-Sasson et al., 2019; Tavassoli et al., 2014; Tomchek & Dunn, 2007), and span across all sensory modalities: touch (Mikkelsen et al., 2018), taste (Tavassoli & Baron-Cohen, 2012b), smell (Okumura et al., 2019; Tonacci et al., 2017), vision (Simmons et al., 2009) and audition (Bonnel et al., 2003).

A framework to define sensory processing difference

To describe sensory differences, a broad range of terminology has been used within autism research, such as '*sensory sensitivity*', '*sensory reactivity*' and '*sensory responsivity'*. Inconsistent use of terminology can lead to confusion and hinders the progression of our understanding of sensory processing differences in autism (He et al., 2023), for example, when the same terminology is used for different aspects of sensory processing. This can lead to a phenomenon known as the 'jingle fallacy', where distinct concepts are wrongly assumed to be the same because they have the same name. He et al. (2023) propose a taxonomy for sensory differences in autism to overcome the inconsistent terminology use in research (see Fig. 1.10). This framework will be used throughout the thesis to integrate different sensory processing measures across studies researching autistic and non-autistic individuals.

The proposed taxonomy is made up of 5 hierarchical levels: 1. Sensory related neural excitability; 2. Perceptual sensitivity; 3. Physiological reactivity; 4. Affective reactivity to sensory input; 5. Behavioural responsivity to sensory input.

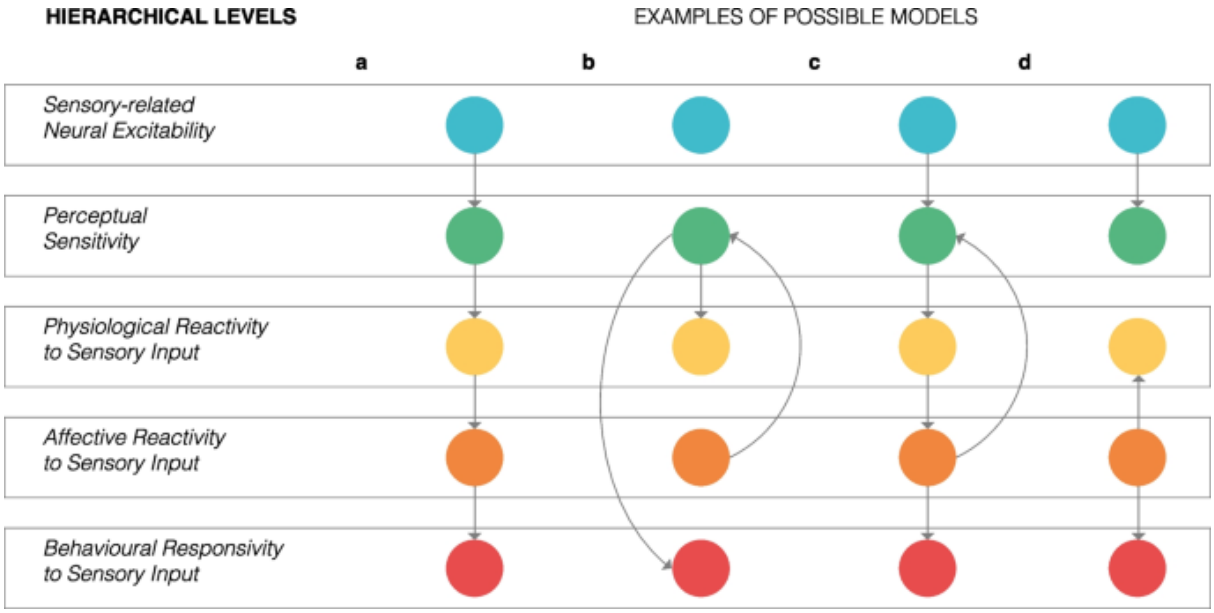

Figure 1.10 Hierarchical framework of sensory processing in autism. Models a-d represent potential models of the interactions between different levels. Figure from He et al. (2023)

Sensory-related neural excitability reflects neural activity in response to stimulation. When neural activity increases, this would be considered neural hyperexcitability, whereas reduced neural activity would be considered neural hypoexcitability. Neural excitability can be measured in animal models of autism and humans using various neuroimaging techniques. For example, one study shows that autistic children have less neural habituation to pure tones than controls, showing evidence of neural hyperexcitability (Cary et al., 2024). *Perceptual sensitivity* describes an individual's ability to detect and discriminate sensory input, usually measured with psychophysical tasks or questionnaires. For example, one study shows that autistic adults have similar olfactory detection thresholds to non-autistic controls, indicating neither perceptual hypersensitivity nor hyposensitvity (Tavassoli & Baron-Cohen, 2012a). While a person may show enhanced perception of a stimulus, that does not necessarily mean they will appraise it as negative or positive nor will they always show a different behavioural response to it. Stimulus appraisal is therefore captured by both physiological reactivity and affective reactivity to sensory input. *Physiological reactivity* involves changes in physiological parameters, such as heart rate, blood pressure or electrodermal activity, to sensory input. For instance, one study found that autistic children have stronger skin conductance reactions to tones that non-autistic children (Chang et al., 2012). *Affective reactivity*, on the other hand, refers to the subjective rating of whether a stimulus is pleasant or unpleasant. Interestingly, affective reactivity is not always related to perceptual sensitivity (Z. J. Williams et al., 2019), confirming that these are indeed be separate concepts. Lastly, *behavioural responsivity* refers to the overt behaviours, or lack thereof, in response to sensory input. A behavioural response to an unpleasant stimulus, as indicated by affective reactivity, might be to physically avoid it by running away for example or putting on headphones. A

behavioural response is still distinct from an affective one, as an individual may find something unpleasant without showing any overt reaction. This aspect is often assessed through questionnaires, like the Infant and Toddler Sensory Profile (ITSP; (Dunn, 2002)), where caregivers might be asked if their child avoids certain foods or smells.

To illustrate, imagine a group of people in a forest. One person, Mike, hears a birdcall far away, but no one else in the group does, indicating Mike has perceptual hypersensitivity. They get closer and more people start to hear the sound. Mike's heart rate goes up when he hears the birdcall, showing physiological hyperreactivity, and he tells the group that he finds the sound very unpleasant whilst others find it just mildly annoying, indicating affective hyperreactivity. Mike then puts on his headphones to drown out the sound, showing behavioural hyperresponsivity. If we had EEG equipment in the forest, we might have been able to distinguish increased activity in Mike's auditory cortex compared to the rest of the group, showing evidence of neural hyperexcitability.

Measuring sensory processing in infants

On each level of He's framework, I have illustrated with an example how sensory processing can be measured, such as psychometrics, electrodermal activity etc. Most commonly though, sensory processing differences are assessed through subjective reports, likely due to the ease of administration and the ability to evaluate sensory symptoms against a normative sample (Yeung & Thomacos, 2020). In infancy and childhood, these assessments often rely on caregiver reports. In addition, clinical observations are used, such as the Sensory Assessment for Neurodevelopmental Disorder (SAND) (Siper et al., 2017) and the Autism Diagnostic Observation Schedule (ADOS) (C. Lord, 1999).

In infancy and toddlerhood, a widely used questionnaire is the Infants/Toddler Sensory Profile (ITSP;(Dunn, 2002)), or its shortened version, the short sensory profile (SSP (Tomchek & Dunn, 2007)) or the second edition, the Sensory Profile 2 (SP-2(Dunn, 2014)). In this questionnaire, caregivers rate the frequency of their child's behaviour on a 5-point scale. According to Dunn's model, different sensory profiles result from differences in neurological thresholds. This is in turn reflected in the behaviour of the child. High neurological thresholds result in sensory hyposensitivity, which is manifested as a failure to notice or respond to sensory stimulation. Low neurological thresholds on the other hand correspond to sensory hypersensitivity and are displayed as high awareness of sensory stimulation and high responsiveness to sensory stimulation. Dunn further divides behaviours into active or passive. Seeking and avoiding behaviours are defined as active behaviours, while registration and sensitivity are categorized as passive behaviours. Dunn's model thus describes four behavioural quadrants to score a child on: Sensory seeking, Low registration, Avoidance and Sensory sensitivity

(Dunn, 2014). Autistic children tend to score higher on all four quadrants of the ITSP compared to typically developing children (Little et al., 2018).

Dunn's model illustrates how terminology around sensory processing can sometimes cause confusion. For example, Dunn uses the term 'Sensory sensitivity' to describe the ability to detect and respond to stimuli passively. From the description, it seems that this measure partly reflects stimulus detection thresholds, at the perceptual sensitivity level in He's framework. However, the individual questions in the 'Sensory sensitivity' quadrant tend to tap into emotional and behavioural response to stimulation rather than the mere detection of them (E.g. 'My child gets fussy when exposed to bright lights'). Dunn assumes that this reflects lower detection thresholds for stimuli, which might be so, but is not directly tested with the ITSP. In the context of He's framework, scores on any quadrant of the ITSP are likely best suited to assessing affective reactivity and behavioural responsivity. In Chapters 2, 3, and 5, the ITSP will be used to assess an infant's sensory profile, and interpreted as a measure that reflects both affective reactivity and behavioural responsivity.

Sensory processing in the first year of life in EL-infants

This section outlines differences in sensory processing between infants at TL and EL for autism in the first year of life. Findings will be organised according the levels of He's framework and measures used to assess sensory symptoms will be highlighted.

A few studies have looked at neural responses to stimulation comparing infants at EL for autism to infants at TL. Guiraud et al. (2011) found that 9-months old EL infants show reduced habituation repeated sounds compared to infants at TL. This is also true for infants at EL for autism that receive an autism diagnosis at three years (Kolesnik et al., 2019). Moreover, 10-month-old infants at EL for autism show decreased gating of tactile input compared to TL, which also predicted later autism traits (Piccardi et al., 2021). These paradigms measure sensory gating by comparing activity to repeated stimuli. When pairs of stimuli are presented with fixed inter-stimulus intervals, such as in Piccardi's study, the response to the second stimulus, which is highly predictable and therefore less relevant for the individual, is typically attenuated – a phenomenon known as repetition suppression (Nordt et al., 2016). We will use this same measure, tactile repetition suppression in Chapter 2.

These studies show a convincing picture of altered sensory-related neural excitability in infants at EL-ASD, likely preceding other behavioural manifestations of autism. Interestingly, while Piccardi et al. (2021) found a difference in neural markers depending on autism likelihood status, they did not find a difference in body movements or screen directed looking after a stimulus between the two groups. This suggest that neural hyperexcitabilty does not necessarily translate into behavioural hyperresponsivity.

As early as 6 months, infants at EL for autism who went on the receive an autism diagnosis at three years show differences in behavioural responsivity, measured through observations (Estes et al., 2015; Sacrey et al., 2015). Using caregiver report, infants at EL show atypical sensory behaviours – both hyper- and hypo – compared to TLs in most quadrants of the ITSP (Mulligan & White, 2012; Van Etten et al., 2017). Wolff et al. (2019) find from 12 months onwards, sensory hypersensitivity, measured with the Sensory Experiences Questionnaire, differed significantly between infants at EL who were later diagnosed with autism, EL infants who were not diagnosed with autism and TL infants, with highest sensitivity scores for EL infants with autism. It is possible these differences are visible earlier, but the study did not include any earlier timepoints. These studies indicate that in the first year of life, differences at the level of *behavioural responsivity* and *affective reactivity* to sensory input emerge between infants at EL and TL, with more unusual behaviours in both the hyper- and hypo-direction.

In conclusion, in the first year of life, infants at EL already show altered sensory processing compared to infants at TL. From 8 months onwards, infants at EL show sensory-related hyperexcitability, however, it is still unclear whether differences are visible earlier than 8 months. Sensory processing captured by caregiver report of observed behaviour also indicates differences between EL- and TL-infants, but again it is not clear when those differences emerge precisely in the first year of life. Interestingly, while neural response indicate *hyper*-excitability, behavioural assessments capture both *hypo*- and *hyper*-responsivity to sensory input in EL-infants.

1.3.1.2. Onset of sleep difficulties in autism

Sleep difficulties are one of the most common co-occurring symptoms in autistic individuals, with prevalence estimates ranging widely from 11% to 80% (Hodge et al., 2014; Souders et al., 2017). The wide range of prevalence estimates is likely due in part to variations in measurement methods, the age range of the participants, and the type of sleep problems studied (Deliens & Peigneux, 2019). A large study in 2- to 5-year-olds found that 53% of autistic children have sleep problems compared to 32% of typically developing children (Krakowiak et al., 2008). Although sleep difficulties are also common in typically developing children, they generally tend to decrease over time, whereas in autistic children, these sleep difficulties often persist or even worsen (Verhoeff et al., 2018).

Reported sleep problems in autism vary considerably, including sleep disordered breathing and parasomnias. However shorter sleep duration, longer sleep onset latency and more night awakenings are consistently reported (Deliens & Peigneux, 2019). In agreement with subjective reports, objective polysomnography studies find shorter total sleep time, prolonged sleep onset latency and more frequent night awakenings in autistic- compared to non-autistic individuals (See review (Petruzzelli et al., 2021)).

Already in the first year of life, sleep difficulties are more prevalent in infants at EL than infants at TL for autism. At 5-, 10- and 14 months-of-age, infants at EL for autism show worse sleep compared to TL, based on a composite measure of caregiver reported night sleep, capturing sleep onset problems, night sleep duration and frequency of night wakings (Begum-Ali et al., 2023). MacDuffie et al., (2020) found that caregivers of 6- to 12-month-old infants at EL who went on to develop autism reported more sleep onset problems. Nguyen et al., (2018) did not find an association with sleep onset time, but did find that more night awakenings predicted autism symptoms in infants at EL.

To our knowledge, no studies in infants at EL have used polysomnography before 12 months-of-age. However, in 13-30 month-olds, Page et al. (2020) used polysomnography to study differences in NREM spectral power. They found that theta (5-7.25 Hz) and fast sigma (15-16 Hz) power were decreased and beta (20-25 Hz) power was increased in autistic toddlers compared to non-autistic peers. During wakefulness, increased beta and gamma (25-70 Hz) are thought to reflect an imbalance in excitation/inhibition in the brain (Orekhova et al., 2007). In typically developing children, theta peak frequency and power during sleep increase in the first years of life (Novelli et al., 2016). Page et al. suggest these differences represent a neurodevelopmental delay in the autistic group. Thus, while sleep differences seem to be present in the first year of life in infants at EL, the biological origin remains unclear.

Understanding the origins and mechanisms that underlie sleep problems is important because poor sleep exacerbates behavioural manifestations of autism, such as increasing communication difficulties or stereotypic behaviour (S. Cohen et al., 2014; Mazurek et al., 2019), and decreasing cognitive performance (Limoges et al., 2013). Autistic children with insomnia also utilise health services twice as much as those without insomnia (Solomon et al., 2022). In addition, there is evidence that caregiver's well-being is impacted by poor sleep (Eyuboglu & Eyuboglu, 2020), which may in turn amplify infant sleep difficulties, resulting in decreased sleep duration and increased night awakenings (Sidor et al., 2013; Sinai & Tikotzky, 2012; Sorondo & Reeb-Sutherland, 2015).

Multiple potential biological causes for sleep problems in autism have been identified, most likely overlapping and with amplifying effects (Deliens & Peigneux, 2019; Lorsung et al., 2021) : 1) Aberrant synaptic functionality - Sleep is highly dependent on normal synaptic functioning and synaptogenesis and synaptic plasticity rely in turn on good sleep (Tononi & Cirelli, 2014; Wang et al., 2011), 2) abnormal sleep-regulating hormones, such as atypical melatonin production (Wu et al., 2020), 3) circadian rhythmicity disruptions, such as mutations in core clock genes (Lorsung et al., 2021), as well as 4) sensory dysregulation.

However, sleep difficulties are not unique to autism, and are prevalent in a number of neurodevelopmental conditions, such as ADHD (Cortese et al., 2009), down syndrome and fetal alcohol spectrum disorder (Kamara & Beauchaine, 2020). Recently, more researchers have been advocating for a transdiagnostic approach that groups individuals based on symptoms rather than diagnosis, both for therapeutic and research purposes (Chawner et al., 2023). It is possible that sleep difficulties originate from similar causes across conditions.

The high variability in sleep difficulties within autism along with their prevalence across a range of neurodevelopmental conditions, suggests that multiple pathways likely lead to different aspects of sleep difficulties. Thus, understanding the origin of sleep difficulties in autism may benefit from a transdiagnostic approach.

In this thesis, I will explore the association between sensory processing and sleep in infants at TL and EL for autism, focussing on sensory symptoms. This approach allows for a more accurate understanding of how sensory processing impacts sleep, irrespective of whether an autism diagnosis is made. This could potentially benefit a wider range of infants with sleep difficulties, regardless of their diagnostic status. In the studies presented in this thesis, infants at EL for autism were recruited, but infants that were additionally at elevated likelihood for ADHD, a commonly co-occurring condition, were not excluded, as our main aim is to investigate sleep in relation to sensory processing. In the following section, I will review the current literature that examines the association between sensory processing and sleep difficulties and emerging theories on the nature of this association.

1.3.2 The relationship between sleep and sensory processing differences

In section 1.1, I discussed that most sensory input is processed by the thalamo-cortico-thalamic loop (see Fig. 1.1), but that this is modulated by vigilance state, with more sensory gating during sleep (Coenen & Vendrik, 1972). However, this same system also modulates the influx of sensory input during various wakefulness states, such as attention (Livingstone & Hubel, 1981). It is possible that differences in sensory gating during sleep between individuals reflect broader differences in sensory processing that could also manifest as sensory differences during wakefulness. Here, I summarize whether sensory differences measured during wakefulness are related to sleep difficulties.

Cross-sectional studies consistently report an association between sensory processing differences and sleep difficulties in neurotypical infants (Appleyard et al., 2020), toddlers and children (Hartman et al., 2022; Kılıç et al., 2024; Vasak et al., 2015), and adults (Engel-Yeger & Shochat, 2012). This association is also evident in autistic children (Hollway et al., 2013; Mazurek & Petroski, 2015; Tzischinsky et al., 2018a) and adults (Hohn et al., 2019), suggesting a common mechanism linking sleep and sensory issues regardless of autism diagnosis. While some studies demonstrate that sleep problems are

related to particular sensory modalities, such as the tactile (Appleyard et al., 2020; Tzischinsky et al., 2018a) or visual modality (Appleyard et al., 2020), overall findings across studies are mixed (Lane et al., 2022).

Regarding the direction of these effects, most studies in both autistic (Hohn et al., 2019; Mazurek et al., 2019; Mazurek & Petroski, 2015; Tzischinsky et al., 2018a) and non-autistic (Appleyard et al., 2020; Vasak et al., 2015) individuals report that *hyper*responsivity is associated with greater sleep difficulties. However, one study finds the opposite relationship: that *hypo*- rather than *hyper*-responsivity is related to greater sleep difficulties, though this finding was marginal and based on a small sample size of just seven hyposensitive individuals (Jamioł-Milc et al., 2021). This indicates a particular link between heightened responsivity to sensory input and sleep difficulties. This association is not limited to a single type of sleep problem but extends across various aspects of sleep, such as total sleep time (Manelis-Baram et al., 2021), overall measures of sleep disturbance (Tzischinsky et al., 2018a), sleep onset time (Appleyard et al., 2020; Vasak et al., 2015) and night awakenings (Mazurek & Petroski, 2015).

In these studies, sensory processing is typically assessed using subjective reports of behavioural or affective manifestations of sensory responsivity, most commonly the ITSP. Similarly, sleep is predominantly captured through subjective reports, the most popular one being the Children's Sleep Habits Questionnaire (CSHQ)(Owens et al., 2000). Studies investigating other aspects of sensory processing and objective measures of sleep are scarce, but there are a few. For example, Reynolds et al. (2012) measured physiological reactivity to sensory input, using electrodermal activity. Regardless of autism diagnosis, poor sleepers had higher levels of electrodermal activity in response to an array of sensory input from all modalities compared to good sleepers. Good and bad sleepers were distinguished based on caregiver report. Using polysomnography, a study in non-autistic adults showed that individuals who rated themselves as sensitive to sensory input indeed showed differential responses to sensory input during sleep (Lechat et al., 2021). Sensitive individuals produced less evoked K-complexes to louder noises compared to non-sensitive individuals during sleep. This shows that affective hyperreactivity during wakefulness is also reflected in how individuals respond to sensory input during sleep. Since evoked K-complexes are thought to promote sleep in response to sensory input (see section 1.1.1.), less frequent sleep promoting responses to sensory input could explain why sensitive individuals experience sleep difficulties, such as waking up frequently at night. These studies show promising results that may help elucidate why hyperresponsivity and sleep problems are associated.

Lane et al. (2022) conducted a review of 24 studies examining the relationship between sensory processing and sleep in autistic individuals and concluded there was substantial evidence that both symptoms co-occur. It is possible that a causal relationship exists between these factors, but research investigating this is still needed. However, pilot intervention studies indicate that alleviating sensory symptoms slightly improves sleep (Cullen et al., 2005; Gringras et al., 2014; Silva et al., 2007), suggesting a causal relationship may exist.

In summary, heightened sensory responsivity appears to be linked to sleep difficulties, from infancy to adulthood. Various aspects of sleep seem to related to sensory processing atypicalities that span across all modalities. Both in autistic and non-autistic individuals, sleep difficulties are accompanied by sensory processing differences, suggesting an underlying mechanism that is independent of autism diagnosis. Three potential scenarios (or a combination of them) explain why both factors may co-occur in the same individuals (see Fig. 1.11): 1. Sensory processing atypicalities cause sleep problems; 2. Sleep difficulties induce sensory processing atypicalities; 3. Sleep difficulties and sensory atypicalities co-occur, driven by a common underlying mechanism.

1.3.2.1 Potential mechanisms that link sleep and sensory processing differences

1.3.2.1.1 Sensory processing differences lead to sleep difficulties

Sensory gating

One plausible mechanism of how sensory processing differences could result in sleep difficulties is through atypical gating of sensory input (Deliens & Peigneux, 2019). As discussed in section 1.1.1, a network of sub-cortical structures typically ensures that the processing of sensory stimuli is attenuated, facilitating sleep initiation and maintenance (Gent et al., 2018). In the same section, the reduced flow of sensory input to the cortex was introduced with the term sensory gating. Attenuated repetition suppression is believed to reflect aberrant sensory gating mechanisms and is therefore particularly relevant to the study of difficulties in initiating and maintaining sleep. Indeed, adult poor sleepers, show less repetition suppression in pre-sleep wakefulness compared to good sleepers (Milner et al., 2009).

Correlational studies have described associations between behavioural manifestations of hyperresponsivity, one potential consequence of reduced gating of sensory input, and sleep difficulties. An intuitive interpretation of this is that hyperresponsive or -reactive individuals do not gate sensory input effectively, which is why they have trouble falling and staying asleep. However as described above in section 1.3.1.1., behavioural manifestations of sensory responsivity are not necessarily a direct consequence of neural excitability. Whether reduced gating explains the link

between behavioural hyperresponsivity and sleep initiation and maintenance difficulties has not been studied to the best of our knowledge.

Sensory processing and stress

Another related – but distinct – hypothesis, is that sleep difficulties arise due to higher physiological arousal caused by behavioural hyperresponsivity. Specifically this theory suggest that sensory stimuli are perceived as averse and therefore activate the hypothalamic-pituitary-adrenal (HPA) - axis, resulting in a state of hyperarousal (Mazurek & Petroski, 2015). The HPA axis has a modulatory role in arousal and sleep regulation. In healthy sleepers, HPA axis activity is low at sleep initiation, while awakenings at night are accompanied by an increases in cortisol, the end product of the HPA axis (Buckley & Schatzberg, 2005). Overactivity of the HPA axis would cause hyperarousal, which has been suggested as a potential mechanism for sleep problems in insomniacs, who have heightened cortisol levels (Dressle et al., 2022). Whether HPA axis activity is actually disturbed in autism is still unclear, as is the link with sleep problems in autism (Dell'Osso et al., 2022). In support of this theory, Richdale et al. (2014) found that autistic adults who self-reported higher pre-sleep arousal, as well as higher anxiety, had longer sleep onset latencies and shorter sleep duration measured by actigraphy. Also, physiological reactivity to sensory input measured by electrodermal activity, was higher in poor sleepers than good sleeper, irrespective of autism diagnosis (Reynolds et al., 2012). Additionally, electrodermal activity, salivary cortisol levels and sensory profiles together accurately predict whether children are good or poor sleepers. This suggests physiological hyperreactivity associates with sleep difficulties, however, no conclusions can be drawn about a causal relationship from these studies.

1.3.2.1.2 Sleep difficulties lead to sensory processing differences

A second plausible mechanism is that sleep difficulties induce or exacerbate sensory atypicalities. Indeed, there is some evidence from studies in non-autistic people that sleep affects sensory experiences the next day. Sleep deprivation increases reactivity in the somatosensory cortex and predicts increased pain experiences (Krause et al., 2019). In addition, sleep deprivation impairs sensory gating (Zhang et al., 2019), and extending sleep in healthy habitually short sleepers normalizes their sensory gating response (Gumenyuk et al., 2013).

It is also possible that disrupted early sleep interferes with the development of the neural circuitry underlying sensory systems. Emerging research suggests that early sleep disruptions drive or exacerbate symptoms of autism, amongst which sensory processing atypicalities (Doldur-Balli et al., 2022; Medina et al., 2023; Wintler et al., 2020). For example, Medina et al. (2023) propose that sleep disruptions in early critical windows interfere with synaptic plasticity and brain development leading to hardwired changes in the brain. Indeed, disrupted early sleep leads to altered somatosensory cortex

development in prairie voles (Jones et al., 2019) and nociceptive sensitivity in adolescent mice (Araujo et al., 2018).

In conclusion, sleep difficulties may play a significant role in the development and exacerbation of sensory atypicalities, both through immediate effects on sensory processing and by influencing the long-term development of neural circuits underlying sensory systems.

1.3.2.1.3 Sleep and sensory differences are caused by the same underlying mechanisms

A third possible mechanism is that sleep and sensory processing difficulties develop independent of each other but as the outcomes of the same underlying factor. I will briefly describe two potential candidates that may influence both sleep and sensory processing, and that are related to autism.

One potential biological mechanism driving both sleep and sensory processing differences is disrupted GABA-ergic functioning. GABA, the main inhibitory neurotransmitter in the brain, is important for sleep onset and maintenance (Gottesmann, 2002) and as mentioned in section 1.1.3., is also crucial for the typical manifestations of sleep rhythms such as sleep spindles. The TRN is the main producer of GABA in the brain and essential for sleep spindle production. In addition, sensory processing is also highly dependent on GABA and a balance between Excitation and Inhibition (E/I) in the brain (Carcea & Froemke, 2013). In autistic individuals, GABA dysfunction is related to processing atypicalities in the tactile (Puts et al., 2017) and auditory (Huang et al., 2023) domain. Thus, disrupted GABA-ergic functioning may be a key factor linking sleep disturbances and sensory processing differences.

Another possibility is that synaptic dysfunction underlies both sleep problems and sensory processing atypicalities. As outlined in section 1.1.2, sleep and in particular SWS, depends on and drives healthy synaptic functioning according to the SHY. Interestingly, dysregulation of synaptic plasticity has been proposed as one of the mechanisms leading to autism itself (Bourgeron, 2015; Guang et al., 2018). Evidence corroborating this theory comes from studies looking at risk genes for autism that are involved in the formation and elimination of synapses and synaptic plasticity (Guo et al., 2017; Veatch et al., 2017). In addition, post-mortem brain studies of autistic individuals show atypicalities in synaptic anatomy, such as increased synaptic density and immature synapses (Hutsler & Zhang, 2010; Irwin et al., 2001). Recently, it has been suggested that synaptic dysfunction may drive both sleep difficulties and other symptoms of autism, placing sleep difficulties as a core symptom of autism (Doldur-Balli et al., 2022; Missig et al., 2020). See figure 1.11 for a summary of the three possible relationships between sleep and sensory processing.

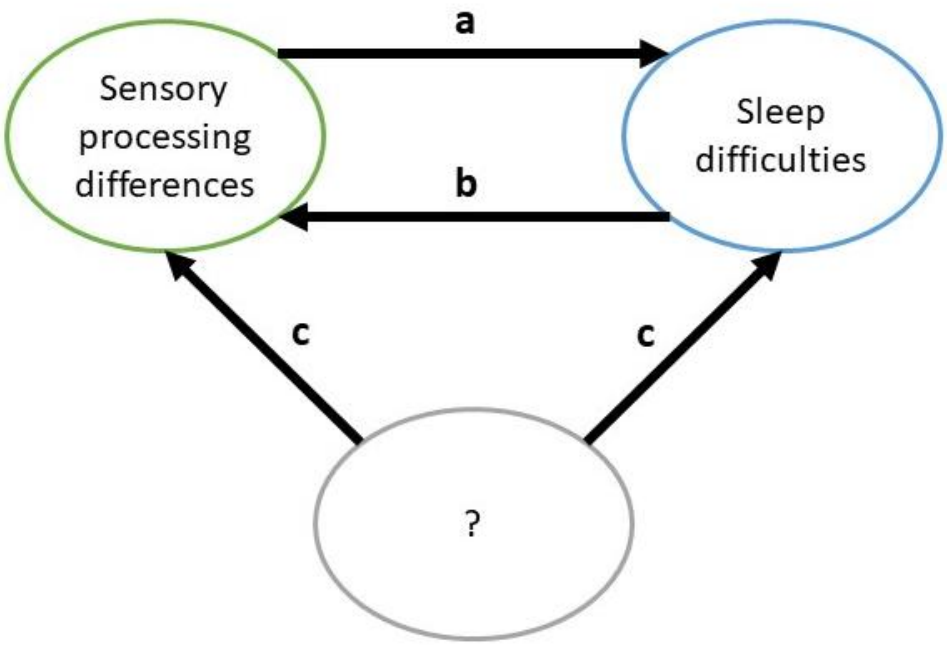

Figure 1.11 Three possible pathways explaining the co-occurrence of sensory differences and sleep difficulties. Sensory processing difference may cause sleep problems (a), sleep problems may cause sensory processing differences (b) or they may arise independently and an underlying mechanism may cause sleep problems and sensory differences (c)

1.4 Overview of the thesis

In this thesis, I investigate evidence in support of a causal relationship from sensory processing differences to sleep difficulties, and a potential role for aberrant gating of sensory input. I ask whether sensory processing differences drive sleep difficulties and whether this is due to altered sensory gating during sleep. Across the thesis, sleep will not be characterised as one entity, but rather dismantled into subcomponents which are most closely connected to sensory processing, focussing on macro-elements of sleep such as awakenings and sleep onset, and micro-elements, like sleep spindles and slow waves. Another central theme of this thesis is the emphasis on infancy. Investigating sleep and sensory processing differences as they first emerge is crucial for understanding how these symptoms interact. Moreover, as discussed in Section 1.2.4, sleep plays a particularly important role during infancy, making it crucial for the development of interventions to focus on this early window in order to achieve the greatest impact.

In the second chapter, I test whether the relationship between sensory hyperresponsivity and sleep difficulties extends to the neural level of sensory processing. In particular, I test whether prolonged sleep onset and more frequent night awakenings are associated with decreased repetition

suppression, measured during wakefulness. Before doing so, I describe the trajectories of sleep onset and night awakenings in infants at TL and EL for autism in the first year of life.

In the third chapter, the directionality between sensory processing differences and sleep onset and maintenance is explored in the first year of life, using caregiver reports. Here, I ask whether sensory differences predict later sleep or vice versa, using a longitudinal design, with data at 5, 10 and 14 months.

The fourth chapter focusses on adapting methodologies to measure sleep EEG features in infancy. I discuss the development of sleep spindles and K-complexes in infancy and the implications for their automatic and visual detection. In particular, adaptations to an existing adult algorithm to detect sleep spindles in infants are discussed, alongside an approach to detect evoked K-complexes in infancy.

The fifth chapter explores whether markers of sensory disconnection during sleep, SWs, K-complexes and sleep spindles, are affected by an infant's sensory profile. Additionally, I ask whether sensory input during sleep affects those oscillations and whether there is an interaction with an infant's sensory profile. To do so, a within-person experiment was conducted, measuring an infant nap with and without auditory stimulation.

The sixth and last chapter, the findings of all chapters are summarised. Then the theoretical implications are discussed as well as the practical implications for studying infant sleep and sensory processing. Finally, I discuss whether we find support for our main question: Is sleep disturbed in infants with sensory processing differences due to poor gating of sensory input?

1.5 The studies behind the datasets

All analyses in this thesis are based on two main datasets that are part of longitudinal studies. In Chapter 2 and 3, secondary data was used from the BASIS study. Chapter 4 and 5 are based on primary data collection from the SNOOSE study. Both studies had aims beyond what is presented in this thesis. To provide context for the experimental chapters that follow, I will offer a brief overview of both studies.

1.5.1 The BASIS study

The BASIS (**B**ritish **A**utism **S**tudy of **I**nfant **S**iblings) network, founded in 2008, aims to study infants that are at elevated likelihood (EL) for autism. They investigate prospective measures of brain function and behaviours in infants at EL for autism and a control group of infants at typical likelihood (TL), with the aim to develop earlier interventions. Infants were recruited at 5 months of age and followed up until they were 7 years old. In this thesis, I use a small part of a large battery of measures that was collected between 2013 and 2018, at 5, 10 and 14 months of age.

1.5.2 The SNOOSE study

The SNOOSE (**S**e**N**s**O**ry **O**rigin of poor **S**leep in **E**arly development) study was part of a Wellcome Trust grant that started in January 2020 (my PhD started in October 2020). Pilot studies were delayed due to the Covid-19 pandemic. The first data was collected in May 2021, when the research labs were re-opened at the University of East Anglia. The SNOOSE study recruited 8 to 10-month-old infants that had an older sibling, either autistic or non-autistic. Similar to the BASIS study, these infants were classified as infants at EL and TL for autism, respectively. Infants that had on older sibling on the waiting list for an autism diagnosis were also included.

Aim of the SNOOSE study

The SNOOSE study aimed to understand the effects of sensory processing differences, common in autistic individuals and infants at EL for autism, on sleep difficulties and the potential knock-on effects on memory consolidation and learning. In this thesis, I focus solely on sensory processing and sleep.

Study procedure and collected measures

The SNOOSE study consisted of three visits: two visits when infants were 8-11 months-old and a follow-up visit at 24 months (see Fig. 1.12). In the **first two visits** an infant nap was recorded using polysomnography in two conditions: a baseline and stimulation condition, of which the order was counterbalanced. In the stimulation condition, auditory input was played in pairs during sleep. The aim of using pairs rather than singletons was to understand whether repetition suppression was also present during sleep. The nap was followed by a study during wakefulness, where EEG was recorded during a tactile gating task whilst infants watched a video clip of the movie fantasia. This task was

added to replicate earlier findings of Piccardi et al. (2021) and understand mechanisms of predictive coding in infants at EL for autism (not included in this thesis). Caregivers were sent questionnaires before the visit and were asked to fill out additional questionnaires during the visit. Before the visit caregivers kept a sleep diary for a week, filled out the Ages and Stages Questionnaire (Squires & Bricker, 2009) and Infant Behaviour Questionnaire (Putnam et al., 2014). Depending on the sleep arrangements in the lab, caregivers filled out a battery of questionnaires whilst the infant napped. Otherwise, questionnaires were sent to the caregivers via email to fill out at home. These included questionnaires about the caregiver themselves assessing sensory symptoms (Adult Autism Spectrum Quotient (Baron-Cohen et al., 2001)), the Glasgow Sensory Questionnaire (Robertson & Simmons, 2013)), about the older sibling(s) (Social Communication Questionnaire (Bölte et al., 2008)) and the infant itself (Infant Sleep Habit Questionnaire (Dias et al., 2018), Infant Toddler Sensory Profile 2 Questionnaire (Dunn, 2014, p. 2)).

When the infants turned 24 months, all participants (including those who only completed one visit at the first timepoint) were invited for a **follow-up visit**. During this visit, toddlers participated in a developmental assessment: the Mullen Scales of Early learning (Mullen, 1995). The aim of this third visit is to understand the predictive effects of early sleep on later development. At the time of submission of this thesis, four infants still need to turn 24 months and return for the last visit.

Figure 1.12 The SNOOSE study in action. Visits 1 and 2 at 8-11 month of age (A-C) and visit 3 at 24 months (D). A. Preparing the EEG cap before the nap. During sleep auditory input is played from the two speakers next to the arm chair. B. Sleeping infant in mother's arms. C. After the nap, an infant watches a cartoon while paired vibrations are delivered to the soles of their feet to measure tactile gating. D. At the follow-up visit a toddler participates in the Mullen Scales of Early Learning.

Data collection for the SNOOSE study started in May 2021 and will end in October 2024. Over the course of these three years, data collection has been completed with the help of students, research assistants and post-docs: Hope Fincham, Dr. Achilleas Pavlou, Dr. Dominic Mclean, Fabiola Ruiz Castro, Morgan Whitworth, Emily Hurst and Giulia D'Avino.

In Chapter 5, I address one of the main aims of the SNOOSE study: Is there a sensory origin of sleep difficulties in early development? I ask whether sleep macro- and micro-architecture differ between the baseline and stimulation condition, and whether this is dependent on an infant's sensory profile. Before answering the theoretical questions, I discuss automated methods to detect micro-architecture events, sleep spindles and K-complexes, and why adaptations may be needed to measure these in infant populations reliably in Chapter 4. I then present how I adapted automated detection of micro-events for the SNOOSE age range.

Chapter 2.
Sensory Gating and Sleep

2.1 Introduction

In Chapter 1, we reviewed the growing body of literature that demonstrates that sleep and sensory processing difficulties are correlated, both in autistic and non-autistic individuals and that this association emerges early in development. I outlined a few potential pathways that could give rise to this association, summarized in Fig. 1.11. This thesis mainly focusses on one potential pathway: whether sensory processing differences *lead* to sleep difficulties due to diminished sensory gating. Previous work has used a variety of sleep and sensory processing measures, some of these being composite measures combining various aspects of sensory processing and of sleep. In this Chapter, I focus on whether sensory gating predicts sleep initiation and maintenance. Results presented in this Chapter are published in Scientific Reports (De Laet et al., 2022).

As described in Chapter 1, one way to quantify sensory gating is by comparing neural responses to repeated stimuli. An identical stimulus, presented at predictable time intervals, is expected to elicit an attenuated response, this phenomenon is called repetition suppression. Piccardi et al. (2021) found that neural repetition suppression to tactile input is diminished in 10 month-old infants at EL for autism compared to infants at TL. Using the same dataset, we ask whether decreased neural repetition suppression to tactile stimulation, measured at 10 months-of-age, associates with parent-report measures of sleep in infants at TL and EL for autism.

Furthermore, we focus on two aspects of sleep, which may be particularly affected by diminished sensory gating: sleep initiation and maintenance (Coenen, 2024). These will be measured as sleep onset latency, the time it takes to fall asleep, and the frequency of night awakenings, assessed through caregiver report. These measures are consistently reported to be elevated in autistic individuals (Deliens & Peigneux, 2019). Typically developing infants take less time to fall asleep and wake up less at night, as they develop (Henderson et al., 2010; Joseph et al., 2015). There is some indication that these features of sleep are altered within the first year of life in infants at EL for autism. Sleep onset latency is longer in 6- to 12-month-old infants at EL who went on to develop autism (MacDuffie et al., 2020) and more night awakenings at 12 months predict more severe later autism traits (A. Nguyen et al., 2018). However it is unclear when these differences start to emerge.

Our first aim is to characterize developmental changes in infants' ability to initiate and maintain sleep by looking at *sleep onset latencies* and *number of night awakenings* at 5, 10, and 14 months of age and testing the point at which EL and TL sleep trajectories diverge. Differences between infants at TL and EL for autism could result both from genetic differences between the two groups as well as from environmental differences, e.g. having an older autistic sibling may disturb their sleep patterns. The second key aim is to test, for the first time, whether an EEG marker of tactile repetition suppression is

associated with individual variation in sleep in infants at TL and EL for autism. If such association exists, it would support the hypothesis that sleep atypicalities in infants with EL for autism are intrinsically driven, rather than a result of their environment. Additionally, we will test whether this association holds even when the group of infants that went on to develop autism are removed. An affirmative answer will be in line with previous work suggesting the link between sensory issues and sleep is not specific to autism (Appleyard et al., 2020). Lastly, we test whether sensory gating predicts sleep over and above subjective scores of an infant's sensory behaviours. Here we aim to understand whether sensory gating explains the commonly reported association between sensory profiles and sleep difficulties. These are additional analyses that are not included in the peer-reviewed paper.

2.2 Methods and Materials

2.2.1 Participants

One hundred and twenty four infants took part in a longitudinal study running from 2013 to 2019 at 5, 10, and 14 months (the BASIS study). The experimental protocol was approved by the National Research Ethics Service (13/LO/0751) and the Research Ethics Committee of the Department of Psychological Sciences, Birkbeck, University of London (13/1617). All experiments were performed in accordance with relevant guidelines and regulations. Parents provided informed, written consent before the onset of the study. The study recruited participants with a first degree relative with autism and/or ADHD. As the focus of the current study is understanding autism-related atypicalities in sensory processing and sleep, infants with a family history of only ADHD were not included. Participants were classified as infants at EL for autism if they had a first-degree relative diagnosed with autism by a licensed clinician (n=97, female=45). Infants with no first-degree relatives with an autism diagnosis and a typically developing older sibling were classified as infants at TL for autism (n=27, female=9). Infants at TL were recruited from a volunteer database at the Centre for Brain and Cognitive Development, Birkbeck University of London. At the 10-month visit, infants (n=65; EL=48, TL=17), participated in an EEG study measuring responses to tactile stimulation. The sample size for particular analyses varied due to missing responses or attrition (see Table 2.1 and 2.3).

Table 2.1 Characteristics of participants included in data analysis at 5-, 10- and 14-month assessments. Means (standard deviation); [a] independent t-test; [b] Pearson Chi square test.

	EL	***TL***	***p-value***
5 month visit			
Age in days	176 (20)	179 (14)	.463 [a]
Number of awakenings	2.00 (1.48)	2.44 (1.47)	.209 [a]
N	65	25	
M:F	35:30	18:7	.117[b]
Sleep onset latency in min	12.42 (10.35)	11.15 (10.10)	.604 [a]
N	65	24	
M:F	34:31	17:7	.117 [b]
10 month visit			
Age in days	319 (15)	322 (17)	.430 [a]
Number of awakenings	1.95 (1.37)	1.27 (1.08)	**.032** [a]
N	81	22	
M:F	46:35	15:7	.335 [b]
Sleep onset latency in min	11.45 (7.51)	7.92 (6.19)	**.041** [a]
N	82	22	
M:F	46:36	15:7	.307 [b]
Tactile Suppression Index	-0.009 (0.212)	0.141 (0.141)	**.008**[a]
N	51	17	
M:F	24:27	10:7	0.401[b]
14 month visit			
Age in days	450 (19)	448 (18)	.548 [a]
Number of awakenings	1.87 (1.46)	1.00 (1.45)	**.022** [a]
N	83	19	
M:F	44:39	12:7	.423 [b]
Sleep onset latency in min	13.18 (11.40)	6.46 (7.25)	**.002**[a]
N	84	19	
M:F	45:39	12:7	.448 [b]

2.2.2 Measures

Sleep measures. Questions from the Sleep and Settle Questionnaire (SSQ) (Matthey, 2001) were used as measures for sleep onset latency and the number of awakenings. The number of awakenings indicates the number of times the infant woke up during the night on average in the preceding week. Integers were required for analysis of this ordinal variable (see Analytical approach 2.2.3), therefore where parents filled in a range instead of one number, the average was taken and, in case of a non-integer, the value was truncated (e.g. 2.5 would become 2). Parents reported separately on the time it took to settle their infant for day (5am to 6pm), evening (6pm to 10pm) and night sleeps (10pm to 5am), again, with an average estimate over the preceding week. If parents reported a range, the mean was taken. We averaged day, evening and night values to create a continuous sleep onset latency

measure. Participants were also included if they only filled in one or two of the questions, since not all infants take two additional naps. However, this was less than 10% of the total participants included in the calculation of sleep onset latency at all three visits.

Autism diagnosis. At 3 years, infants at EL were assigned a best estimate research diagnosis autism (EL-ASD+) or non-autism (EL-ASD-) according to the DSM-5 diagnostic criteria by experienced researchers with the help of a licensed clinical psychologist (GP and TC). The decision was based on outcomes from the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) (C. Lord et al., 2000), Autism Diagnostic Interview-Revised (ADI-R) (C. Lord et al., 1994), Mullen Scales of Early Learning (MSEL) assessments (Mullen, 1995), the Vineland Adaptive Behaviour Scales (VABS) (Sparrow & Cicchetti, 1989) and researcher observations during previous visits.

EEG Paradigm. A full description is reported in Piccardi et al. (2021).

Stimuli

Custom built voice coil tactors were attached to the bare soles of each foot of the infant with cohesive tape. Vibrotactile stimuli were delivered to both feet simultaneously with a frequency of 220Hz. Stimuli lasted 200ms and were consistently presented in pairs (S1–S2) with a 500ms interstimulus interval (Figure 2.1). The time between pairs of stimuli, the intertrial interval, varied randomly between 8-12s. In total, 38 pairs of stimuli were administered split across two 4 minute blocks with a 2 minute break in between. As a distraction, a visually engaging cartoon without language content (Fantasia by Walt Disney) was played during the experiment. Infants were seated on the lap of the parent 60 cm from the screen in a dimly illuminated room.

Apparatus and time-frequency analysis of EEG

EEG was recorded using 124 channels of a 128-channel HydroCel Geodesic Sensor Net connected to a NetAmps 400 amplifier (Electrical Geodesic, Eugene, OR) and referenced online to the vertex (Cz). Net station (Electrical Geodesic) was used to pre-process the EEG data offline. If individual epochs exhibited voltage changes over 200 µV in one segment (identified by automated artefact detection), individual channels within segments were eliminated after additional visual inspection. Artefact free EEG segments were processed and analysed using EEGLAB (v.13.4.3b) in MATLAB®. Spectral decompositions were conducted using *Wtools* (developed by E. Parise, L. Filippin, & G. Csibra, available upon request), employing complex Morlet wavelets 3-20Hz with 1Hz resolution. A continuous wavelet transformation of all segments was conducted, and the absolute value of the results was extracted. A 100 ms pre-stimulus window was used as a baseline. Individual epochs were averaged per participant. Time-frequency decomposition was used to quantify oscillatory alpha amplitude desynchronization to tactile stimulation (i.e. 6–10-Hz alpha amplitude during the task as

compared to alpha amplitude at baseline). The average 6–10-Hz alpha desynchronization oscillatory amplitude was extracted from two 500-ms-long windows time-locked to S1 and S2 offset. A tactile suppression index (TSI) was computed by subtracting alpha amplitude desynchronization at S1 from alpha amplitude desynchronization at S2.

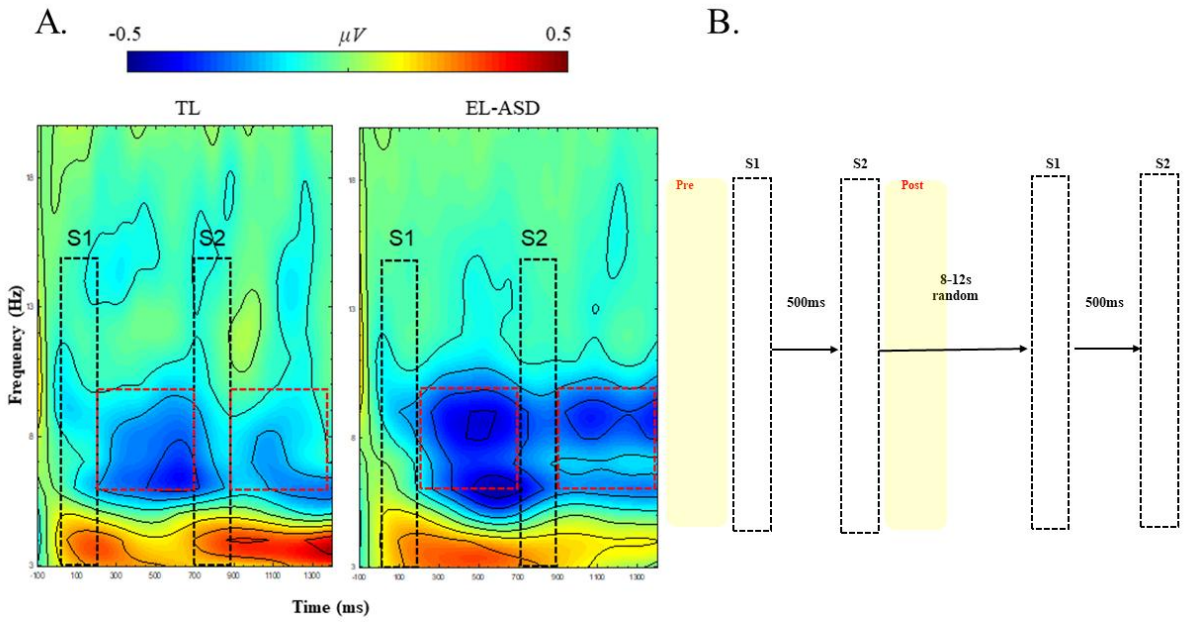

Figure 2.1 ***A.*** *Time frequency plots in both groups, TL and EL. Black dotted lines indicate the first (S1) and second (S2) stimuli. Red dotted lines indicate the 500-ms-long time-windows post-stimulus offset selected for statistical analysis. Amplitude scale is−0.5, 0.5μv.* ***B.*** *Experimental design. Vibrotactile stimuli are presented in pairs (S1 and S2) with a fixed interstimulus interval of 500ms. The interval between the onsets of pairs of stimuli ranged from 8 to 12s randomly. Figures adapted from Piccardi et al., (2021) and created using WTools (Parise & Csibra, 2013).*

Sensory profile measure. Infant's sensory profiles were measured as *low threshold* (LT), a combination of the sensory sensitivity and sensation avoidance quadrants from the ITSP (Dunn, 2002). These two quadrants are chosen because they are consistently correlated with sleep difficulties (Manelis-Baram et al., 2021) and are conceptually most relevant to the study of sleep onset and maintenance. A low threshold for sensory stimulation, rather than a high threshold, could lead to hyperarousal and trouble falling and staying asleep (Riemann et al., 2010). On the ITSP, caregivers indicate the frequency of their child's behaviour on a five-point scale ranging from almost always to almost never. LT contains questions from five modalities: general, auditory, oral, touch and vestibular. LT was reverse scored, so a high score reflects high behavioural and affective reactivity to sensory stimulation. The ITSP was collected at all three timepoints of the study. In this Chapter, we will only use concurrent measures of LT and sensory gating at 10 months. In the Chapter 3, the bi-directional links between LT and sleep measures will be modelled longitudinally. At 10 months LT consists of 23 questions (see Appendix B table A.3), of which the average was taken.

2.2.3. Analytical approach

Statistical analysis was performed in SPSS v25. Three values of sleep onset latency (2 EL; 1 TL), one value of the number of awakenings (TL) and one value of the TSI (EL) were more than three standard deviations above the mean and trimmed to one integer above the highest value. To analyse the trajectory of sleep onset latency and the number of awakenings, generalized estimating equations (GEE) were used factoring in Group and time of the measurement (Visit). GEE was chosen to model the non-normal response variables and to accommodate for missing data. For number of awakenings, a count variable, a Poisson distribution with a log-link was specified. Due to a right skew for the sleep onset latency variable (see table 2.2 for skewness and normality), a gamma distribution with log-link was specified. An integer of 1 was added to the sleep onset latency variable, so values of zero would not be omitted in the GEE. Maximum likelihood was selected for scale parameter estimation. The structure of the working correlation matrix was specified as 'unstructured' with a robust estimator.

Table 2.2 Skewness and normality values of sleep onset latency at 5, 10 and 14 months.

Sleep Onset Latency	**Kolmogorov-Smirnov**	**df**	**Sig**	**Shapiro-Wilk**	**df**	**Sig**	**Skewness (SE)**	**Kurtosis (SE)**
5 months	0.179	66	0.000	0.840	66	0.000	1.78 (0.26)	3.64 (0.51)
10 months	0.128	66	0.009	0.927	66	0.001	0.78 (0.24)	0.36 (0.47)
14 months	0.218	66	0.000	0.814	66	0.000	1.59 (0.24)	2.75 (0.47)

To assess the main effects of Visit (5, 10 and 14 months) and Group (EL and TL), the GEE was run with main effects only and then a Group*Visit interaction was added in a separate step, from which the interaction terms are ascertained. Post hoc Bonferroni corrected pairwise comparisons were run for significant main effects of Visit. In case of a significant interaction with Visit, a separate GEE was run per timepoint to assess group differences. GEE models were run to test whether the TSI was associated with the sleep parameters, first concurrently (i.e. at 10 months), then longitudinally. To test the generalisability of results across the EL group, all analyses were repeated after removing infants who were subsequently diagnosed with autism at 36 months. We also excluded infants at EL who did not come to the 36 month assessment and therefore could not be assigned to EL-ASD+ nor EL-ASD-. The concurrent models at the 10-month timepoint were rerun with LT as an additional predictor.

Table 2.3 Sample sizes of the analyses with EEG data per model. Sleep Onset Latency (SOL); Night awakenings (Awa); Tactile Suppression Index (TSI); Typical likelihood (TL); Elevated Likelihood (EL); EL with a confirmed autism diagnosis (EL-ASD+); EL without an autism diagnosis (EL-ASD-).

Model	Concurrent		Longitudinal	
Outcome	SOL (10 mo)	Awa (10 mo)	SOL (14 mo)	Awa (14 mo)
Covariates	Group, TSI (10 mo)	Group, TSI (10 mo)	Group, TSI (10 mo), SOL (10 mo)	Group, TSI (10 mo), Awa (10 mo)
Total n (m:f)	58 (31:27)	58 (31:27)	50 (27:23)	49 (26:23)
TL(m:f)/EL(m:f)	15(9:6)/43(22:21)	15(9:6)/43(22:21)	11(7:4)/39(20:19)	11(7:4)/38(19:19)
TL/EL-ASD-/EL-ASD+/missing	15/34/5/4	15/34/5/4	11/30/5/4	11/29/5/4

2.3. Results

2.3.1. Sleep trajectory

The number of awakenings significantly decreased each consecutive visit in the whole sample (see Figure 2.2, Waldχ^2 = 10.503, p = .005) with post hoc pairwise comparisons indicating that infants had significantly fewer awakenings at 14 months (estimated mean [EM] = 1.63; 95% confidence interval [CI] = 1.36, 1.97) compared to 5 months (EM = 2.14; CI = 1.84, 2.50; p = .004, Bonferroni corrected p = .05/3). There was no significant main effect of autism likelihood status on awakenings (Waldχ^2 = 1.116, p = .291), but there was a significant interaction between visit and autism likelihood status (Waldχ^2 = 10.777, p = .005); post-hoc tests revealed no significant group difference in awakenings at 5 months (Waldχ^2 = 1.773, p = .183), but a significant difference at 10 months with infants at EL waking more often (Waldχ^2 = 5.068, p = .024), and a marginally significant difference, in the same direction, at 14 months (Waldχ^2 = 3.465, p = .063).

For sleep onset latency, there was no significant main effect of visit (Waldχ^2 = 2.567, p = .277), nor did autism likelihood status reach significance (Waldχ^2 = 2.850, p = .091). However, the interaction between visit and autism likelihood status was significant (Waldχ^2 = 17.421, p < .001). Post-hoc tests showed no significant differences at 5 months (Waldχ^2 = .273, p = .601), but significantly longer sleep onset latencies at 10 months in infants at EL compared to infants at TL (Waldχ^2 = 4.402, p = .036), which persisted at 14 months (Waldχ^2 = 7.545, p = .006).

Looking at the sleep trajectory by group (see Figure 2.2), the number of awakenings (Waldχ^2 = 13.239, p = .001) and sleep onset latency (Waldχ^2 = 15.272, p < .001) significantly decreased with age in infants

at TL, while in infants at EL they remained stable over time (Waldχ^2 = 1.753, p = .416 and Waldχ^2 = 3.787, p = .151, respectively). In TL infants, post hoc tests indicated that the number of awakenings was significantly higher at 5 months (EM = 2.47; CI =1.97, 3.09) compared to 10 months (EM = 1.36; CI = 0.94, 1.97; p = .001, Bonferroni corrected) and 14 months (EM = 1.09; CI = 0.64, 1.86; p < .001, Bonferroni corrected). TL infants' sleep onset latency also significantly decreased from 5 months (EM = 12.62 mins; CI = 9.28 mins, 17.16 mins) to 14 months (EM = 7.93 mins; CI = 5.53 mins, 11.37 mins; p = .001 Bonferroni corrected), but not from 5 to 10 months (EM = 7.94 mins; CI = 5.45 mins, 11.59 mins; p = 0.096).

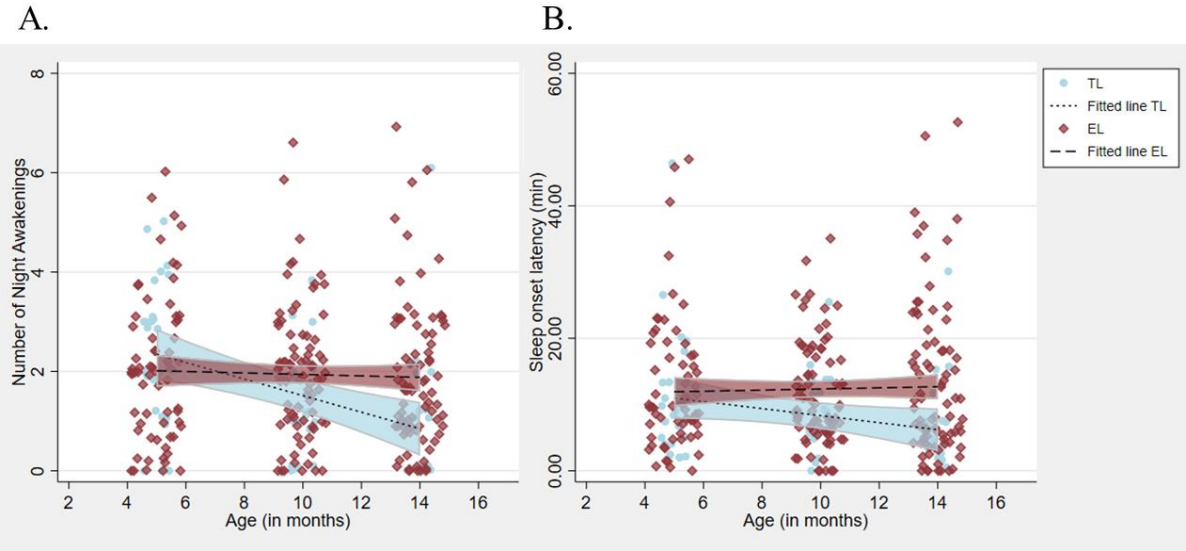

Figure 2.2 Sleep trajectories from 5 to 14 months. Infants at typical likelihood for autism (TL) are depicted in blue and infants at elevated likelihood for autism (EL) are depicted in red. Fitted lines are shaded by the 95% confidence interval. ***A.*** *The number of night awakenings.* ***B.*** *Sleep onset latency.*

Sleep trajectories split on autism likelihood and - diagnostic status

Infants at EL (n=82) were assessed for autism at a subsequent 36-month visit; 12 infants met diagnostic criteria for autism (EL-ASD+) and 70 infants did not (EL-ASD-) (see Appendix A for descriptives). When the sleep trajectory analyses were re-run by splitting the data in groups based on autism outcome (TL vs EL-ASD- and TL vs EL-ASD+), the small EL-ASD+ group (n=12) tended to have the most extreme values (see figure 2.3). The number of awakenings was significantly affected by visit and decreased with time (Waldχ^2 = 7.633, p = .022). There were no group effects for TL versus EL-ASD- (Waldχ^2 = .522, p = .470) or EL-ASD+ (Waldχ^2 = 1.459, p = .227). However, there was a significant interaction between visit*EL-ASD- (Waldχ^2 = 10.510, p = .005) and visit*EL-ASD+ (Waldχ^2 = 9.260, p = .010). Neither TL versus EL-ASD- (Waldχ^2 = 2.430, p = .119; EL-ASD-: n = 47) or EL-ASD+ (Waldχ^2 = 0.044, p = .833, EL-ASD+: n = 10) had a significant effect on the number of awakenings at 5 months. At 10 months EL-ASD- had significantly more night awakenings than TL infants (Waldχ^2 = 4.663, p = .031; EL-ASD-: n = 62), but EL-

ASD+ did not (Waldχ^2 = 2.021, p = .155; EL-ASD+: n = 10). However, at 14 months the results were reversed and EL-ASD+ has significantly more night awakenings than TL infants (Waldχ^2 = 7.252, p = .007; EL-ASD+ n = 11), while EL-ASD- did not (Waldχ^2 = 2.563, p = .109; EL-ASD-: n = 64).

In comparison to the TL infants, EL-ASD+ had a significantly longer overall sleep onset latency (Waldχ^2 = 4.379, p = .036) after controlling for visit, whereas EL-ASD- did not differ significantly from TL (Waldχ^2 = .227, p = .634). The interactions of both Visit*EL-ASD- and Visit*EL-ASD+ were significant (Waldχ^2 = 17.173, p < .001; Waldχ^2 = 9.260, p = .010). Post hoc tests revealed that TL infants did not differ from EL-ASD- or EL-ASD+ for sleep onset latency at 5 months (EL-ASD-: Waldχ^2 = .013 , p = .910, p= .812, n= 47; EL-ASD+: Waldχ^2 = 1.137 , p = .286, n = 10), whereas from 10 months EL-ASD+ had significantly longer sleep onset latency (Waldχ^2 = 8.185, p = .004; n = 10), which continued at 14 months (Waldχ^2 = 11.093, p = .001, n = 11). In comparison to TL, EL-ASD- did not have significant different sleep onset latency at 10 months (Waldχ^2 = 1.791, p = .181, n = 62), but they had a significant longer sleep onset latency at 14 months (Waldχ^2 = 6.064, p = .014, n = 65). These results are summarized on figure 2.3.

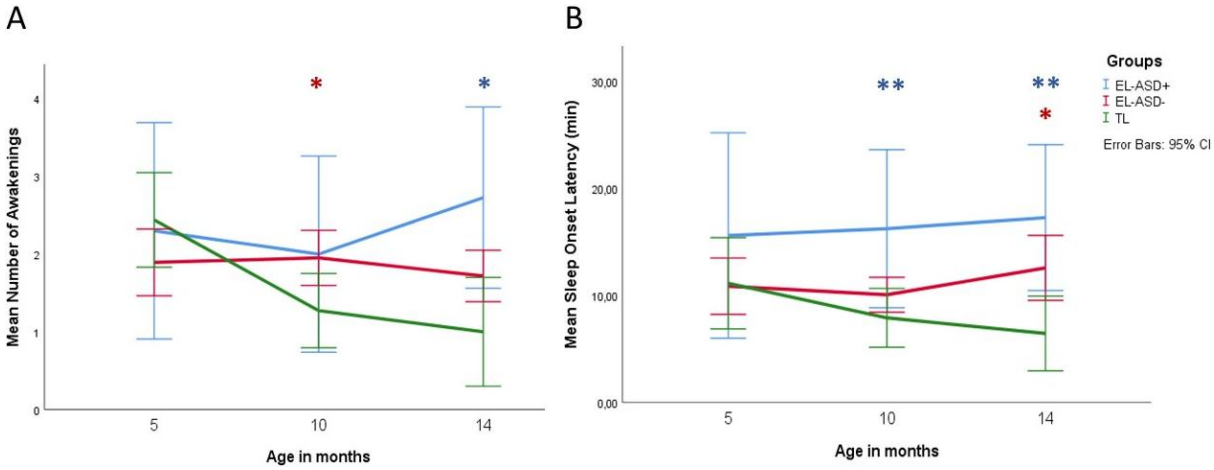

Figure 2.3 Sleep trajectories from 5 to 14 months based on autism likelihood and – diagnostic status. ***A.*** *Number of night awakenings.* ***B.*** *Sleep onset latency. Groups are based on autism diagnosis at 36 months. TL: infants at Typical Likelihood for autism; EL-ASD-: Infants at Elevated Likelihood for autism who were not diagnosed with autism at 36 months; EL-ASD+: Infants at Elevated Likelihood for autism who received an autism diagnosis at 36 months. Stars in red indicate a significant difference between infants at TL and at EL-ASD-. Stars in blue indicate a significant difference between infants at TL and at EL-ASD+. *p < .05. **p = .01 - .001. ***p< .001.*

2.3.2. Associations with tactile repetition suppression

*Table 2.4 Correlation coefficients (Spearman) of all measures used in the analyses. SOL = Sleep Onset Latency; TSI = Tactile Suppression Index; LT= Low Threshold; mo = months. *significant correlation p < .05 (2-tailed). **significant correlation p < .01 (2-tailed)*

	TSI	*Awakenings 5mo*	*Awakenings 10mo*	*Awakenings 14mo*	*SOL 5mo*	*SOL 10mo*	*SOL 14mo*	*LT 10mo*
TSI	1							
Awa 5mo	.107	1						
Awa 10mo	-.075	**.379****	1					
Awa 14mo	-.030	**.386****	**.577****	1				
SOL 5mo	**-.348***	**.208***	.209	.172	1			
SOL 10mo	**-.370****	.042	**.354****	**.360****	**.426****	1		
SOL 14mo	**-.260***	.190	**.288****	**.429****	**.469****	**.631****	1	
LT 10mo	-.117	.044	**.264****	**.286****	**.245***	**.346****	**.234***	1

Scores on the TSI were significantly higher (more suppression of the repeated response) in infants at TL compared to infants at EL (t = 2.717 (66), p = .008) in line with results previously reported by Piccardi et al. (2021) in infants from the same cohort (Table 2.1). Summary correlations between TSI, LT and sleep measures at 5, 10 and 14 months are presented in Table 2.4. To test whether emerging sleep problems associate with the TSI concurrently, two GEE models were run, one with the number of awakenings and the other with sleep onset latency at 10 months as the outcome variable. In both models, TSI and autism likelihood status were entered as predictors. TSI had a significant effect on sleep onset latency (Waldχ^2 = 7.775, p = .005), but not on the number of awakenings (Waldχ^2 = .009, p = .923), see Figure 2.4. Autism likelihood status did not have a significant effect on awakenings at 10 months (Waldχ^2 = 2.616, p = .106) and there was also no significant effect of the interaction between autism likelihood status and TSI (Waldχ^2 = 1.146, p = .284). Autism likelihood status did not have a significant effect (Waldχ^2 = 2.125, p = .145) nor did it significantly interact with TSI (Waldχ^2 = .284, p = .594) in predicting sleep onset latency at 10 months.

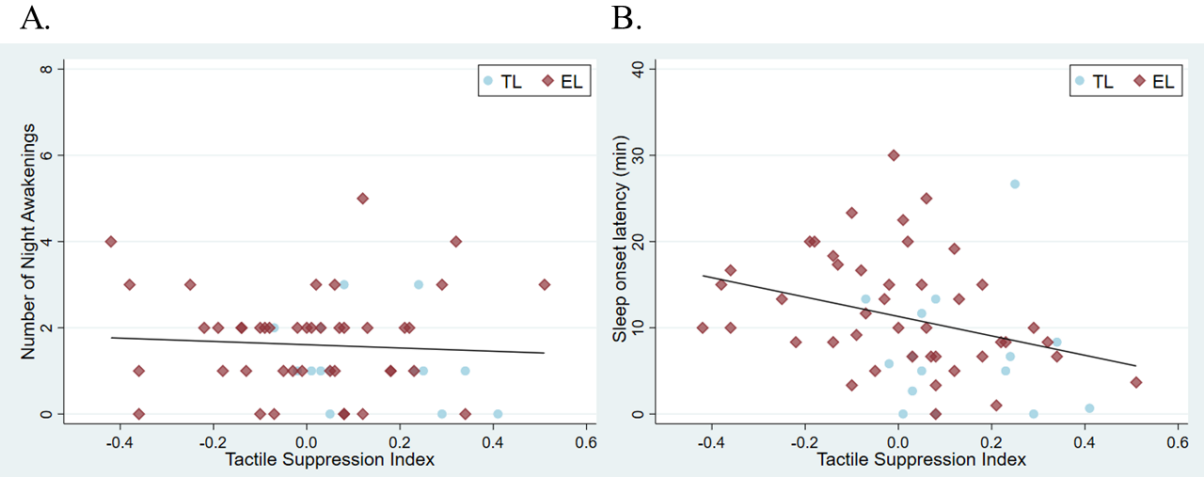

Figure 2.4 Associations with tactile suppression index (TSI) at the 10-month visit. Infants at typical likelihood for autism (TL) are depicted in blue and infants at elevated likelihood for autism (EL) are depicted in red. ***A.*** *The number of night awakenings is not significantly associated with TSI.* ***B.*** *Sleep onset latency is significantly associated with TSI.*

To evaluate if the TSI at 10 months associates longitudinally with the sleep parameters at 14 months, over and above 10-month sleep, separate models were run with 14-month sleep onset latency or number of awakenings as outcomes. In both models TSI, autism likelihood status and the relevant 10-month sleep measure (sleep onset latency/number of awakenings), were entered as predictors. TSI did not significantly associate with the number of awakenings (Waldχ^2 = .128, p = .721) or sleep onset latency at 14 months (Waldχ^2 = .635, p = .425).

We excluded the EL-ASD+ participants (n = 5) and infants who did not come in for the 36-month visit and therefore could not be categorized as EL-ASD+ or EL-ASD- and reran the GEE with infants at TL and EL-ASD-. Identical to the main analysis, GEE was performed to assess the effects of tactile repetition suppression, measured at 10 months, on sleep onset latency and the number of night awakenings concurrently at 10 months and longitudinally at 14 months in two separate models per sleep measure. Removal of the EL-ASD+ group did not change the results substantively (See Table 2.5), suggesting that these infants did not drive the results in the main analysis.

Additionally, we wanted to understand whether poor sensory gating explains the commonly reported association between poor sleep and behavioural and affective hyperreactivity. We therefore investigated whether the TSI predicted sleep measures over and above LT. Indeed, when LT was added to the model, both TSI and LT significantly predicted SOL (respectively, Waldχ2 = 6.406, p =.011; Waldχ2 = 5.719, p = .017), with decreased TSI and higher scores on LT predicting longer sleep onset times. There was no significant interaction between LT and autism likelihood status (Waldχ2 = .006, p = .361). The same model was run with night awakenings as the outcome variable. As before, the TSI did not

significantly predict the number of night awakenings (Waldχ2 = .077, p = .781), but LT did, with high scores on LT predicting more night awakenings (Waldχ2 = 3.973, p = .046). There was no significant interaction between LT and autism likelihood status (Waldχ2 = 2.195, p = .138).

Table 2.5 Summary of results of the concurrent models and longitudinal models with the tactile suppression index (TSI) as a predictor. The first column are the main results with all participants included. The second column are the results of the sensitivity analysis excluding all EL-ASD+ infants and infants without a diagnostic outcome status. In the concurrent models, after removal of the EL-ASD+ infants, a total of 50 infants remained (TL: n = 15: EL-ASD-: n = 35). In the longitudinal models, after exclusion of the EL-ASD+ infants, a total of the total number of 41 infants remained for awakenings (TL: n = 11, EL-ASD-: n = 30) and 42 for sleep onset latency (TL: n = 11, EL-ASD-: n = 31).

	All participants		**Without EL-ASD+**	
	Waldχ^2	p-value	Waldχ^2	p-value
Awakenings 10 mo				
TSI	0.009	0.923	0.003	0.953
Group	2.616	0.106	3.030	0.082
TSI*Group	1.146	0.284	1.299	0.254
Sleep Onset Latency 10 mo				
TSI	7.775	**0.005**	6.833	**0.009**
Group	2.125	0.145	1.378	0.240
TSI*Group	.284	0.594	0.275	0.600
Awakenings 14 mo				
TSI	0.128	0.721	0.012	0.912
Group	8.718	**0.003**	6.014	**0.014**
Awa 10 mo	171.226	**< .001**	36.805	**< .001**
Sleep Onset Latency 14 mo				
TSI	0.635	0.425	0.14	0.708
Group	11.695	**0.001**	11.877	**0.001**
SOL 10 mo	32.530	**<.001**	17.884	**< .001**

2.4. Discussion

Characterising sleep trajectories of infants at TL and EL for autism revealed that sleep onset latency and night awakenings decrease in infants at TL from 5 to 14 months. These patterns mirror previous findings that sleep consolidates during the first year of life in typically developing infants (Henderson et al., 2020). In contrast, no developmental change was seen in infants at EL, leading to significant differences between the groups from 10 months, with longer sleep onset latency and more night awakenings in infants at EL than TL. Further, our results show that an objective measure of poor sensory gating of tactile stimulation significantly associates with longer sleep onset latency. This finding was independent of autism likelihood status, implying that there is a general association between sensory gating and sleep onset latency, in line with previous evidence in typically developing children (Appleyard et al., 2020). No association between sensory gating and number of night awakenings was

found, either suggesting a differential mechanism of sensory gating during pre-sleep wake and sleep itself or simply reflecting unreliable caregiver reports of night awakenings compared to sleep onset latency. We discuss each of these findings in turn, below.

Trajectories of sleep parameters. In a previous paper, using the same cohort of children, Begum-Ali et al. (2023) reported that a composite score of night sleep was worse in infants at EL compared to infants at TL at 5, 10 and 14 months. Here, we specifically focused on two measures of sleep that are expected to be influenced by the ability to gate sensory input - sleep onset latency and night awakenings. Our findings suggest that differences in both of these parameters emerge between 5 and 10 months, which narrows down the developmental interval within which to investigate underlying causes. Using a less precise measure, asking about the presence of frequent night awakenings (3 or more) and not the exact number awakenings, in a longitudinal population study, Humphreys et al. (2014) only found a significant difference in frequent night awakenings between non-autistic and autistic toddlers at 30 months, but not at 6 or 18 months. In our sample, however, infants at EL woke up more frequently than infants at TL from 10 months, suggesting an earlier emergence.

Subdividing the EL infants into those that were or were not subsequently diagnosed as autistic (EL-ASD+ and EL-ASD- respectively) showed that infants at EL-ASD+ took longest to fall asleep, suggesting that sleep onset latency is intrinsically driven in infants at EL for autism, rather than a result of a shared environment with an older autistic sibling. The differences in night awakening trajectories between infants at EL-ASD+ and EL-ASD- were less consistent, likely due to the small sample sizes in the subgroups. Further research is needed to investigate these differences in infants at EL-ASD+ and EL-ASD-.

The impact of sensory gating on sleep. That reduced sensory gating was associated with longer sleep onset latency, but not with more night awakenings is consistent with literature suggesting these sleep processes have different underlying mechanisms. For example, adults with sleep onset problems, showed reduced repetition suppression to auditory stimuli during pre-sleep wake compared to good sleepers, but not during REM or N2 (Milner et al., 2009). In support of different neural mechanisms underlying sleep onset and maintenance, the manipulation of the inhibitory neurotransmitter $GABA_A$ receptor, which has an important role in sleep (Gottesmann, 2002), affected sleep initiation more than sleep maintenance in fruit flies (Agosto et al., 2008). In adult patients with primary insomnia (PI), auditory stimulation did not increase the number of awakenings compared to an undisturbed, baseline night sleep. However, the PI group was more likely to stay in REM sleep when stimulation occurred while controls transitioned to N2 more often (Hairston et al., 2010). Thus, while increased stimulus

input (due to poor gating) might not result in more awakenings, it may still affect sleep quality and architecture to a larger extent in populations with sleep difficulties, like in autism. In Chapter 5, we investigate the effects of sensory input on macro- and micro-architecture features of sleep.

The incongruity of the reported association between sensory gating and sleep onset latency but not awakenings may also reflect the nature of the sensory gating measure used in this study. Sensory gating was measured during wakefulness and may therefore be more closely related to arousibility at sleep onset compared to arousibility from sleep. Kisley et al. (2001) reported differences in sensory gating, although in response to auditory stimulation, dependent on vigilance state in the same individuals. Alternatively, the discrepancy in our findings between awakenings and sleep onset latency could be caused by the accuracy of caregiver report. Sadeh et al., (1996) found that parents reported the number of awakenings significantly less accurately than sleep onset in infants when compared with actigraphy results. Moreover, Pisch et al. (2015) found no significant association between parent reported awakenings and actigraphy in infants.

The association we find between tactile repetition suppression and sleep onset latency may also be indicative of common underlying mechanisms. One possibility is that impaired GABAergic functioning impacts both sensory gating and sleep. GABA is the main inhibitory neurotransmitter in the brain. Altered functioning of GABAergic signalling in autism is evident from lower GABA levels, reduced expression of GABAergic genes and microdeletion in genes coding for subunits of the $GABA_A$ receptor (Coghlan et al., 2012). Both sensory processing atypicalities and sleep onset problems could be triggered by reduced GABA levels. In fact, sleep onset latency was decreased in rats after oral administration of GABA (S. Kim et al., 2019), and mutation of $GABA_A$-receptor in fruit flies resulted in a reduction of sleep onset latency (Agosto et al., 2008). At the same time, Puts et al. (2017) found that reduced sensorimotor GABA-levels in autistic children are associated with sensitivity to touch. Thus, an impaired GABA-ergic system could underlie the co-occurrence of sensory issues and sleep disturbances in autistic individuals. In general, there is accumulating evidence to believe that an excitation/inhibition (E/I) imbalance, particularly relevant during brain development, plays an important role in the pathophysiology of autism. Besides affecting basic sensory processing and sleep, an E/I imbalance disturbs optimal information transmission, which could alter processing of complex information such as social stimuli, resulting in social and cognitive impairments seen in autism. Therefore, while this study shows that poor sensory gating is indeed predictive of longer sleep onset times, it is impossible to infer a causal relationship from these results. In Chapter 3 and 5, we investigate evidence in support of a causal pathway.

In exploratory analyses, we investigated the effects of two different measures of sensory processing on sleep, sensory gating and sensory profiles. Poor tactile gating and high scores on low threshold both predicted longer sleep onset times in the same model, suggesting that they contribute to longer sleep onset but independently of each other. While tactile gating did not predict night awakenings, high scores on low threshold did. This suggests that sensory profiles may capture sleep difficulties more broadly, whereas tactile gating appears to relate to specific aspects of sleep, such as sleep onset.

Interestingly, there was no significant correlation between the two sensory processing measures (see Table 2.4). The lack of correlation between these two measures is perhaps not very surprising as they capture quite distinct aspects of sensory processing. The TSI captures an infant's ability to detect and supress a response to an irrelevant stimulus on a neural level, whereas LT captures a variety of behaviours and emotions in response to sensory input. In addition, LT includes measures of all sensory modalities, while sensory gating was measured in response to tactile stimulation. This not the first study that does not find the expected correlation between different measures of sensory processing. For example, autistic adults that have better perceptual sensitivity for sound had lower, not higher, self-reported auditory sensitivity (M. W. M. Kuiper et al., 2019). As discussed in Chapter 1 section 1.3.1.1, the questions on the ITSP seem to relate mostly to affective reactivity and behavioural responsivity to sensory input in He et al.'s taxonomy of sensory differences (He et al., 2023), which may reflect general anxiety rather than poor sensory gating alone. Anxiety, which is highly prevalent in autism and has been suggested to contribute to sleep problems in autism (Deliens & Peigneux, 2019; Hollway et al., 2013), and is often associated with difficulties in sleep initiation and maintenance (Bourdet & Goldenberg, 1994). A more in-depth study of the relationship between these two measures in needed to understand whether they are truly unrelated or whether this relationship is obscured by the composite nature of sensory profile scores.

Longitudinal effects of sensory gating. TL participants showed a further decrease in sleep onset latency between 10 and 14 months. These changes may, in part, reflect the development of self-soothing strategies. The mechanisms driving individual progress in self-soothing are poorly understood, but it is believed this requires infants to identify body cues for sleepiness and to use behavioural strategies, such as sucking on fingers, to fall asleep more easily (Camerota et al., 2019; Goodlin-Jones et al., 2001) . It is therefore plausible that poor sensory gating may not only delay sleep onset but it may also interfere with the development of these strategies. We found tactile repetition suppression did not predict sleep onset latency at 14 months after controlling for 10-month sleep onset latency. This suggests that the effects of reduced sensory gating on sleep do not accumulate over time. Manelis-Baram et al., (2021) found that changes in sleep disturbances between 3 and 5 years of age were associated with changes in sensory sensitivities specifically, and not with other core autism

symptoms, in autistic children. Similar to our results, they found that initial sensory profile scores did not predict sleep disturbances at a later timepoint, but they did not test whether early sleep predicts later sensory scores. To better understand the directionality of sensory processing and sleep, a longitudinal study design is needed. In the current study, that focussed on sensory gating, we could not assess the directionality between symptoms because sensory gating was only measured at one timepoint. In Chapter 3, we test the directionality of effects between sleep onset and maintenance and sensory profiles, which were collected at 5, 10 and 14 months.

While this study is novel in its use of an objective measure for sensory gating, sleep is captured by caregiver reports and not by more objective measures. The use of actigraphy or polysomnography could greatly improve the reliability of sleep behaviours, particularly for night awakenings. In Chapter 5, we investigate the effect of sensory input on arousal during an infant nap using polysomnography.

Chapter 3.
Longitudinal investigation of sleep and sensory profiles

3.1 Introduction

In Chapter 2, we showed that sensory gating predicts sleep onset latency concurrently, but not night awakenings, confirming that poor sensory gating may explain some of the sleep difficulties seen in infants at EL for autism. However, an infant's sensory profile - their average affective and behavioural responses to sensory input - predicted both sleep onset latency and night awakenings, in combination with sensory gating. Thus, while both sensory processing measures predicted sleep, the reverse direction of association could also be the case: Sleep difficulties could induce or exacerbate sensory responses. Indeed, there is some evidence from studies in non-autistic people that sleep affects sensory experiences the next day. Sleep deprivation increases reactivity in the somatosensory cortex and predicts increased pain experiences (Krause et al., 2019). In addition, sleep deprivation impairs sensory gating (Zhang et al., 2019), and extending sleep in healthy habitually short sleepers normalizes their sensory gating response (Gumenyuk et al., 2013).

Assessing whether there is a directionality in symptom emergence/change could direct effective strategies to improve quality of life for autistic individuals. One way of measuring directionality is by using longitudinal study designs, which take advantage of the temporal ordering of measurements to make inferences about cause and effect (Hamaker et al., 2020). Common statistical methods to do so will be discussed in further detail below. Only a few studies have looked at the longitudinal relationship between sleep and sensory atypicalities in autism. Mazurek et al. (2019) looked at sleep problems and a range of co-occurring symptoms in 2- to 10-year-olds with ASD. Sensory over-responsivity was the only significant predictor of a change in sleep between baseline and follow-up (3.8 years later) in the younger age group, the 2- to 3-year-olds. The result was uni-directional, sleep did not predict a change in sensory over-responsivity. One other study found that auditory processing in typically developing 6-month-olds predicted sleep onset latency at 2.5 years (Appleyard et al., 2020). Unfortunately, they did not have data on sleep at the 6-month time-point in order to test whether early sleep predicts sleep onset latency at 2.5 years. Manelis-Baram et al. (2021) looked at change in sleep disturbances and sensory profiles in children with ASD from 3- to 4.5-years-old. They found that sleep disturbances and sensory sensitivities covary longitudinally. Changes in sensory sensitivity, but not initial sensitivity scores, predicted future sleep disturbance over and above initial sleep disturbances. The study did not look at the opposite prediction. In summary, of the few longitudinal studies that look at sleep and sensory processing, most looked at whether early sensory processing predicted later sleep or a change in sleep, but not the opposite way around. Only Mazurek et al. (2019) tested a possible bi-directional relationship and found a unidirectional association from early sensory processing to later sleep. Nevertheless, results from one study with a limited timeframe, 3 to 4.5 years, is not sufficient to rule out a potential pathway from sleep to sensory processing difficulties. It is possible that good sleep,

particularly during the first year of life drives the development of sensory processing systems. The foundations for sensory neurodevelopment are laid in early life and early sleep plays a key role in the development of the central nervous system (Grubb & Thompson, 2004; Knoop et al., 2021; Whitehead et al., 2018). Assessing whether directionality is present at the onset of symptoms of autism could allude to which symptom initially drives the other.

3.1.1 Statistical approaches to capture reciprocal influences

In essence, this is a causal question, much like many of the key questions in developmental science that ask how different constructs co-develop over time and whether reciprocal relationships exist between them (Curran & Hancock, 2021). How to make inferences about cause and effect appropriately has been a topic of heavy debate (Cartwright, 2007; Hamaker et al., 2020; Zyphur et al., 2020). Besides experimental studies, several methods exist that use longitudinal panel data to make inferences about causality. Initially, researchers began testing causal relationships with longitudinal panel data by simply looking at cross-lagged relationships, taking advantage of the chronological order of events to address causation. The rationale being that, if one value precedes the other in time, the earlier one must be the cause and the latter the effect, assuming that time only travels forward. However, this approach was critiqued because it fails to account for the degree of stability of the constructs (Rogosa, 1980). If one construct is highly stable and the other is not, then seemingly 'causative' associations would appear that are actually due to the stability of the constructs. Rogosa (1980) suggested a more elaborate panel model, the cross-lagged panel model (CLPM), which controls for the stability of constructs. The problem seemed to be resolved and researchers could once again make causal inferences with longitudinal panel data. Until a new critique was delivered. Not only the stability of a construct has to be taken into account, but also the stability of a construct within an individual. Both critiques stem from 'the omitted variable problem'. A 'causal' pathway might appear, but this may be driven by a third unobserved variable that is the root of the cause. If one fails to account for this unknown third variable in the model, then erroneous conclusions about causality could be made. New improvements were suggested to the CLPM with the help of advanced statistical methods such as structural equation modelling (SEM). For an overview of the different statistical approaches that aim to draw more accurate conclusions about causality with longitudinal panel data see Usami et al. (2019). In the section below, the CLPM will be discussed and compared to two more statistically complex models that aim to circumvent the shortcomings of the CLPM, the Random Intercept (RI) -CLPM and the Latent Curve Model with Structured Residuals (LCM-SR).

3.1.1.1 (Random Intercept) Cross lagged panel model

For decades, the CLPM has been used to examine the reciprocal relationship between two or more variables (Rogosa, 1980). Using longitudinal data, this model assesses how a variable Y at one

timepoint (t) can be predicted by another variable X at a previous timepoint (t-1), constituting what is known as the cross lagged relationship (see Fig. 3.1). In the CLPM, stability of measures is accounted for by controlling for variable Y at t-1, known as the autoregressive relationship. In other words, X predicts a change in Y over time. The CLPM also models the opposite relationships and assesses whether Y at t-1 predicts a change in X from t-1 to t.

In 2015, Hamaker et al., published an influential paper (cited 2618 times on 29/03/2024) critiquing the traditional CLPM. They, alongside others (Berry & Willoughby, 2017; Curran et al., 2014), argue that if the stability of the variables over time is to some extent trait-like and time-invariant, the autoregressive relationships of the CLPM fail to account for this. As a consequence, erroneous conclusions about reciprocal effects could be made, if temporal fluctuations are confounded with time-invariant traits (Hamaker et al., 2015). It is not unreasonable to assume some level of individual stability of constructs over time, as many constructs in psychology do have some degree of stability, such as personality types, anxiety, emotional intelligence and mental health to name a few (Carter Leno et al., 2022; Lodder et al., 2022; Zadorozhny et al., 2024). Hamaker et al. (2015) propose an extension to the CLPM, the RI-CLPM (Fig 3.2), which controls for the individual time-invariant stability by separating the between-person variance from the within-person variance, using principles from multilevel modelling. In a multilevel model, data has a hierarchical structure. A classic example of hierarchical data with two levels are test scores of pupils that are nested within classrooms and within schools. By centring the individual scores around the means per classroom and per school, variation that is due to common factors is accounted for. A great strength as well as a methodological challenge of longitudinal data is that it can be treated as hierarchical data, where data is nested within the individual itself over time. To circumvent the issue of confounding factors due to trait-like individual differences, the RI-CLPM extends the CLPM with the addition of a latent variable for each construct, called the random intercept, that draws on the observed variables with factor loadings of 1.

Before elaborating on the mathematical differences between the CLPM and RI-CLPM, let us explore why it necessary to separate within and between person effects from a conceptual standpoint of view. Hamaker (2012) gives a clear example to illustrate why it is not possible to generalize results from the between-person level to the within-person level. Imagine that people who type faster (than others) tend to make less mistakes (than others). This is a finding on the between person level. However, it does not imply that the same is true on a within-person level, so that when an individual types faster than they usually do, they will make less mistakes. In fact, the opposite is more likely. In this scenario, a negative relationship would be expected on the between-person level, but a positive one on the within-person level. In the context of the current study, significant effects on the between-person level would have different implications than effects on the within-person level. E.g. Infants that are more

sensitive compared to others might wake up more at night (between-person level), but that does not mean that if an infant is more sensitive than usual on a particular day, they will wake up more than usual (within-person level). It is often the within-person effects that researchers are actually interested in, when asking causal questions about underlying mechanisms. Of course, that does not mean that effects on the between person level are not valuable or interesting in themselves, but it is crucial that the two levels are not conflated. In both cross-sectional data and the traditional CLPM it is not possible to distinguish the within-person (state-like) aspect from the between-person (trait-like) aspect and to know which of the two drives the results. The variance and correlations obtained in a cross-sectional study rely on the variances and correlations of both the within-person and between-person level. The cross-sectional variance is the sum of the variances at both levels and the correlation is a weighted sum of the within- and between-person correlation. The relative contributions depend on the variance at each level. Only if there is no variance at the between-person level, then the cross-sectional results would coincide with the within-person results.

To clarify the differences between the traditional CLPM and the RI-CLPM, the equations of both models will briefly be compared (for a more comprehensive explanation, see Hamaker et al. (2015)). In the CLPM and RI-CLPM two (or more) constructs, x and y, are modelled in waves over time. For simplicity, just one variable x, will be described further. However, the exact same equations apply for variable y. In a traditional CLPM the measurement x_{it} at time (t) for individual (i) is described as the sum of the mean of all participants at time t (μ_t) and the individual's deviation from this mean at time t (p_{it}) (Equation 3.1). In the RI-CLPM, p_{it}^*, the individual's temporal deviation from the group mean, is divided into two terms: a time invariant stable trait factor κ_i and a temporal deviation from the individual means p_{it}^* (Equation 3.2). κ_i is an individual's trait-like deviation from the temporal group means. p_{it}^* now represents the individual's temporal deviation from their expected scores ($\mu_t + \kappa_i$) rather than from the group means only (μ_t). If there is no stable factor, then κ_i is zero and the RI-CLPM becomes equivalent to the traditional CLPM.

*Equation 3.1 Measurement equation of variable x in the **CLPM***

$$x_{it} = \mu_t + p_{it} \quad (1)$$

*Equation 3.2 Measurement equation of variable x in the **RI-CLPM***

$$x_{it} = \mu_t + \kappa_i + p_{it}^* \quad (2)$$

An individual's temporal deviation from either the group means μ_t in the CLPM or their expected scores ($\mu_t + \kappa_i$) in the RI-CLPM are modelled with structural equations (Equation 3.3 and 3.4). From these we can get the estimates of the autoregressive parameter, α_t or α_t^* , and the cross-lagged parameter, β_t or β_t^*. Although the structural equations of the CLPM and RI-CLPM are similar, the

interpretation of the autoregressive and cross-lagged parameters are different. The autoregressive parameter, α_t , of the CLPM represents the stability of rank order of individuals within the group from one wave to the next, while α_t^*, in the RI-CLPM represents the amount of within-person carry-over effect. E.g. if α_t^* is positive, it implies that the occasions on which a person scored above their expected score are likely to be followed by a score above their expected score again. The cross lagged parameters in a RI-CLPM explain to what extent a deviation from one's expected score on x at t2 can be explained by a deviation from one's expected score on y at t1, whilst controlling for a deviation from one's expected score on x at t1.

*Equation 3.3 Structural equation of the temporal deviation in the **CLPM**.* $q_{i,t-1}$ is the temporal deviation of variable y at the timepoint preceding time t.

$$p_{it} = \alpha_t p_{i,t-1} + \beta_t q_{i,t-1} + u_{it} \quad (3)$$

*Equation 3.4 Structural equation of the temporal deviation in the **RI-CLPM**.* $q_{i,t-1}^*$ is the temporal deviation of variable y at the timepoint preceding time t.

$$p_{it}^* = \alpha_t^* p_{i,t-1}^* + \beta_t^* q_{i,t-1}^* + u_{it}^* \quad (4)$$

A limitation of the RI-CLPM is that growth is not explicitly modelled. However, because the group means at each wave are not constrained over time, the RI-CLPM implicitly allows for growth in the model (Mulder & Hamaker, 2021). However, it may be of interest to know if there is variability in individual trajectories and whether this variability can be explained by another variable of interest. If individual growth is a key interest then another model should be considered, such as the LCM-SR, which will be discussed next.

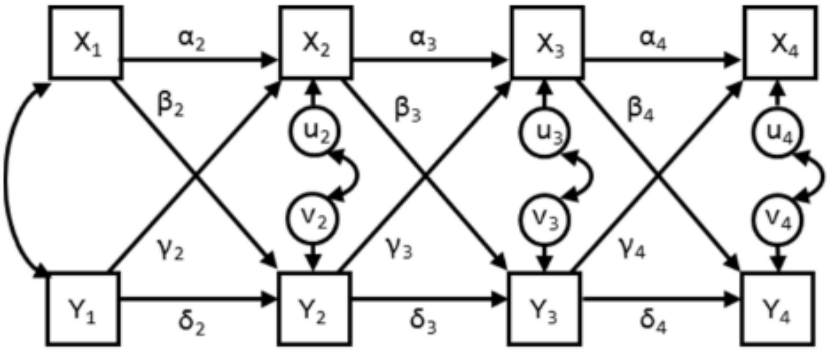

Figure 3.1 Cross Lagged Panel Model (CLPM). Figure from Hamaker (2018).

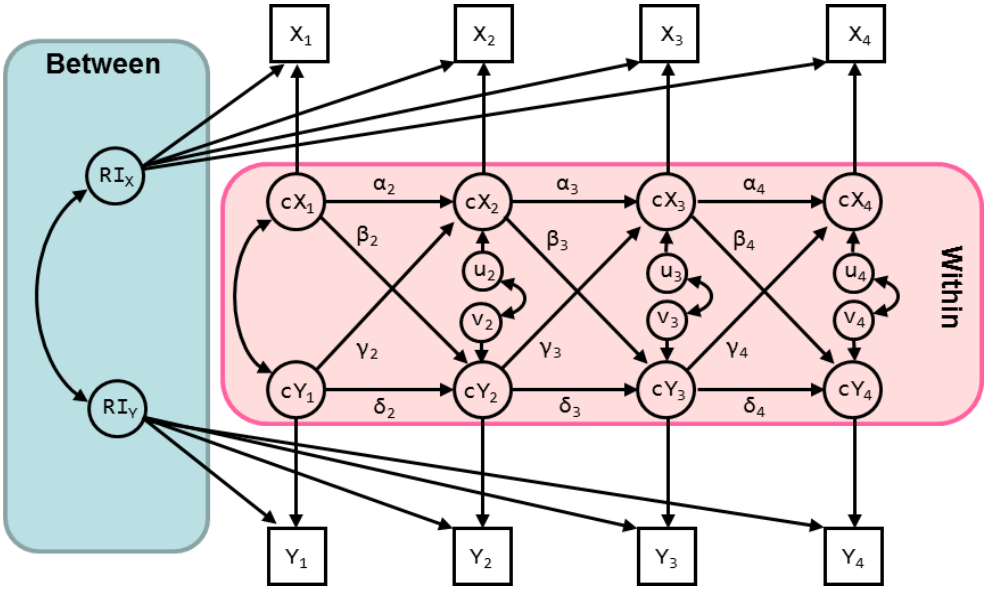

Figure 3.2 Random Intercept – Cross Lagged Panel Model (RI-CLPM). Figure from Hamaker (2018).

3.1.1.2 Latent Curve Model with Structured Residuals

Around the same time as Hamaker et al. (2015), Curran et al. (2014) suggested an approach to separate between- and within-person components using latent curve models with structured residuals (LCM-SR) (Fig. 3.3). In the LCM-SR, an individual's score on an observed variable x at time t is described as the individual regression line with intercept, I_{xi}, and slope, S_{xi} (Usami et al., 2019).The residual x^*_{it}, can be thought of as the timepoint specific deviation from an individual's expected growth curve (Equation 3.5).

*Equation 3.5 Measurement equation of variable x in the **LCM-SR.***

$$x_{it} = I_{xi} + (t-1)S_{xi} + x^*_{it} \quad (5)$$

The LCM-SR consists of two parts, a latent growth model that captures between person differences in stable traits and development, and the CLPM that captures the within person differences. A key difference with the RI-CLPM is that the latent slope factors are modelled as well as the latent intercepts. Just as in a RI-CLPM, the lagged relationships are pure within-person associations, separated from the between-person effects. However, due to the inclusion of the slope factor, the residuals represent the time point specific deviations from the person-specific mean and person specific growth curve. This has implications for the interpretation of the lagged parameters. In a LCM-SR, significant autoregressive parameters indicate that a deviation from the person specific trajectory is enduring over time, a non-significant effect indicates that a deviation from the trajectory does not persist and the individual falls back to the expected trajectory. Significant cross-lagged parameters indicate that a deviation from the person specific growth curve in x at time t is associated with

deviations from the person specific growth curve in variable y at time t+1. In a linear LCM-SR, it is assumed that the means change linearly over time, while the RI-CLPM estimates means per time point and therefore allows for development to take on any shape (Usami et al., 2019). In a LCM-SR, It is possible to model growth curves with other shapes than linear, such as quadratic, but a minimum of 4 waves is needed to do so – in this study we only have 3 waves. Thus a key difference between the two is that growth is explicitly modelled in the LCM-SR, and implicitly included in the RI-CLPM.

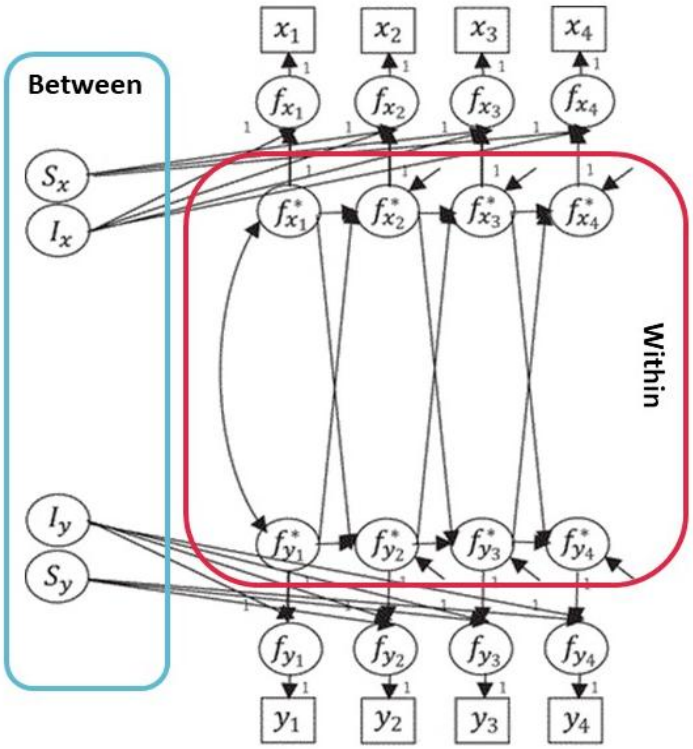

Figure 3.3 Latent Curve Model with Structured Residuals (LCM-SR) with intercept (I) and slope (S) on the between person level. Figure adapted from Usami et al. (2019)

3.1.2 Aim and hypothesis

The aim of the current study is to clarify whether sleep problems influence sensory differences or vice versa, using a longitudinal design with infants who are at EL for autism. Using a prospective sibling design allows us to capture sleep problems and sensory differences as they emerge in infancy. A longitudinal design with three timepoints enables us to separate between- and within-person effects, which no previous studies have attempted before. We ask whether early sensory processing, starting from 5 months, drives a change in sleep 4-5 months later and/or whether early sleep drives a change in sensory processing 4-5 months later. Answering this question will help clarify whether sleep problems and sensory processing atypicalities have a bidirectional or unidirectional relationship at

their onset. Additionally, if effects are only found on the between person level, this would imply there is a third variable driving both sleep and sensory processing difficulties.

In this study, we will run a traditional CLPM and compare its results to models that do separate within- and between person effect, such as the RI-CLPM and LCM-SR. The main difference between the two models is that growth is explicitly modelled in the LCM-SR. Curran & Hancock (2021) recommend adapting the choice of model to both theory and model fit. Therefore, since modelling growth is not the main aim of this study, initially a RI-CLPM will be run. However, a LCM-SR will also be conducted in case it fits the data better. Running the traditional CLPM alongside these models allows us to discuss methodological differences and helps clarify the interpretation of the separation between within- and between-person effects.

These models enable us to tease apart whether sleep difficulties arise as a secondary symptom of autism, driven by sensory atypicalities, or whether they are a core symptom caused by a common biologic and genetic factors as other core symptoms of autism. If there are significant effects on the within person level, either uni-or bi-directional, it would suggest a causal relationship between sleep and sensory issues. If effects emerge on the between person, then common underlying factors likely drives both variables (See section 1.1.2.1.3 for examples of potential common factors).

3.2 Methods

3.2.1 Participants

The dataset used in this chapter is the same as in Chapter 2 from the longitudinal British Autism Study of Infant Siblings (BASIS). The study involved three lab visits when infants were 5, 10, and 14-months-old. A total of 127 infants contributed to the analyses in this Chapter. Three infants were included here who completed the Infant/Toddler Sensory Profile (ITSP), but were excluded in the Chapter 2 due to missing responses on the Sleep and Settle Questionnaire (SSQ). The sample of this study included 100 infants at EL for autism (female : n = 47) and 27 infants at TL for autism (female: n = 10). More detailed information on the BASIS study and recruitment is available in Chapter 2 section 2.2.1.

3.2.2 Measures

3.2.2.1 Sleep measures

Sleep onset latency and number of night awakenings were taken from the SSQ (Matthey, 2001). Sleep onset latency was averaged across daytime and nighttime sleep and was calculated in exactly the same way as in Chapter 2 (See 2.2.2). For night awakenings, parents were asked to report the number of times their child woke up during the night on average in the preceding week. When parents provided a range, the average was taken. As a result of these average values, the variable night awakenings is

treated as a continuous variable, rather than a count variable. Note that in Chapter 2, values were truncated instead and the variable was treated as a count variable there.

3.2.2.2 Sensory processing measure

Sensory processing was measured as low threshold (LT) a combination of the quadrants sensory sensitivity and sensation avoidance from the ITSP (Dunn, 2002)). The age-appropriate version of the ITSP was used at each visit. At 5 months, LT consists of 17 questions, however question 5 '*My child has difficulty getting to sleep and is easily awakened*' was excluded, due to the similarity to the sleep measures used in this study. This results in a total of 16 questions that were averaged at the 5 month wave. At 10 and 14 months the age-appropriate ITSP consists of 23 questions that make up the LT subscale. This version did not have any sleep related questions. See Appendix B for a full list of all questions included at the 5 month timepoint (table A.2) and 10 and 14 month timepoint (table A.3). LT contains questions from five modalities: general, auditory, oral, touch and vestibular. On the ITSP, caregivers indicate the frequency of their child's behaviour on a five-point scale ranging from almost always to almost never. LT was reverse scored, so a high score reflects high reactivity to sensory stimulation, identical to Chapter 2.

3.2.3 Statistical Analyses

As a first step, all variables were checked for outliers using Python version 3.8.13 (Van Rossum & Drake, 2009). Outliers were not eliminated, but Winsorized to reduce their influence. All datapoints that had a z-score above 4 were Winsorized to one value above the next highest value. The points between 3 and 4 SD were checked visually on a scatterplot in relation to other concurrent variables. If the datapoints did not follow the same trend as the other datapoints, they were Winsorized. See Appendix C table A.5 for all datapoints that were above 3 SD. As a result, three values of sleep onset latency were Winsorized (2 EL, 1 TL) and one value of night awakenings (1 EL).

Model specifications

All panel models were performed in MPLUS version 8.5 (Muthén & Muthén, 1998). To test for a bidirectional relationship between LT and sleep, panel models were run for sleep onset latency and night awakenings separately. Three different types of models were run for each sleep variable, a CLPM, RI-CLPM and LCM-SR (see Figures 3.4-3.6). Due to the small sample size and uneven group sizes (EL: n=100, TL: n=27), no multi-group analysis was done, instead autism likelihood was controlled for on each observed variable. There are two possibilities when including a time-invariant predictor, such as autism likelihood, in RI-CLPM or LCM-SR; either the predictor is regressed on each observed variable or on the random intercepts (Mulder & Hamaker, 2021). Because our previous results showed a significant difference between ELs and TLs only from 10 months onwards and not at 5 months, autism

likelihood was regressed on each observed measurement. This allows the effect of autism likelihood on sleep and sensory profiles to differ at each timepoint. Most variables were not normally distributed (see Appendix C table A.6 for Normality, skewness and kurtosis values per variable). In case of non-normality, Finney & DiStefano (2013) recommend using maximum likelihood estimation with robust standard errors and chi-square test statistic. Therefore, a sandwich estimator is applied using the MLR command in MPLUS, which is more robust to non-normality and additionally can handle incompleteness of data under a missing at random assumption.

It is possible to constrain multiple parameters a priori if there are theoretical assumptions to support it or a posteriori based on model fit. A few parameters are commonly constrained to be invariant over time in longitudinal models. One option is to constrain the group means at each time point to be equal. However, the group means are not expected to be the same in a variable that shows a developmental pattern. In Chapter 2, we showed that both sleep onset latency and night awakenings decrease from 5 to 14 months. The group means are therefore not constrained in these models. Other parameters that can be constrained are the lagged parameters, both the cross lags and autoregressive lags, but only if the time between waves is approximately similar (Gollob & Reichardt, 1987; R. M. Kuiper & Ryan, 2018). In this dataset there are 5 months between the first and second wave and 4 months between the second and third wave, which we consider to be similar. Because we did not have any strong predictions of time invariant lagged relationships, unconstrained models were run first. However, if the model did not fit the data properly, parameters were constrained to improve model fit. First, an unconstrained version of each model was run (version a). If the model fit was not acceptable, the autoregressive parameters and cross-lagged parameters were constrained to be time-invariant (version b). When the model fit was still not acceptable, the co-variances were constrained in addition to the autoregressive and cross-lagged parameters (version c).

In models using latent variables – here the RI-CLPM and LCM-SR – additional parameters can be constrained. Typically, observed variables are regressed on their random intercept and constrained to 1, which ensures that all timepoints contribute equally to the latent factor. It is possible to freely estimated the factor loadings, but only with panel data with 4 or more assessment waves (Mulder & Hamaker, 2021). In this study there were only 3 assessment waves, so factor loadings were constrained to 1. In a LCM-SR a slope is added as a latent factor, in addition to a random intercept. The slope is established by setting the factor loadings to be proportional with the time intervals (Curran et al., 2014). The factor loadings were set at 0, 5 and 9 to accurately represent the time between visits, which were at 5, 10 and 14 months.

As a first step, we ran the RI-CLPM - version a to c depending on model fit indices. Then a CLPM was run that was equivalent in terms of constraints to the best fitting RI-CLPM. An equivalent version is needed to compare the results of the models. Lastly, a unconstrained version (a) of a LCM-SR was run to see whether growth could be modelled explicitly.

Model fit

How well the specified model fits the data is commonly assessed by the χ^2 -test of model fit, which compares the observed data to the restricted data of the model. If the test is non-significant then the restricted and observed data are not significantly different, and the model fits the data. However, this test is particularly sensitive to sample size. Models with small sample sizes, such as in this study, may often have non-significant χ^2 tests, because of the lack of power rather than actual 'good fit' of the data (Satorra & Saris, 1985). Because of this, additional fit statistics were consulted to evaluate model fit: Root Mean Square Error of Approximation (RMSEA), Comparative Fit Index (CFI), Tucker-Lewis index (TLI) and the Standardized Root Mean Square Residual (SRMR). The recommended cut-offs for these measures are: RMSEA < .08, CFI >= .90, TLI >= .95 and SRMR <0.08 (Hu & Bentler, 1999). STDXY standardised values are reported throughout the text and on the figures when they were available, otherwise unstandardized values are used. Significance values from the unstandardized results are reported.

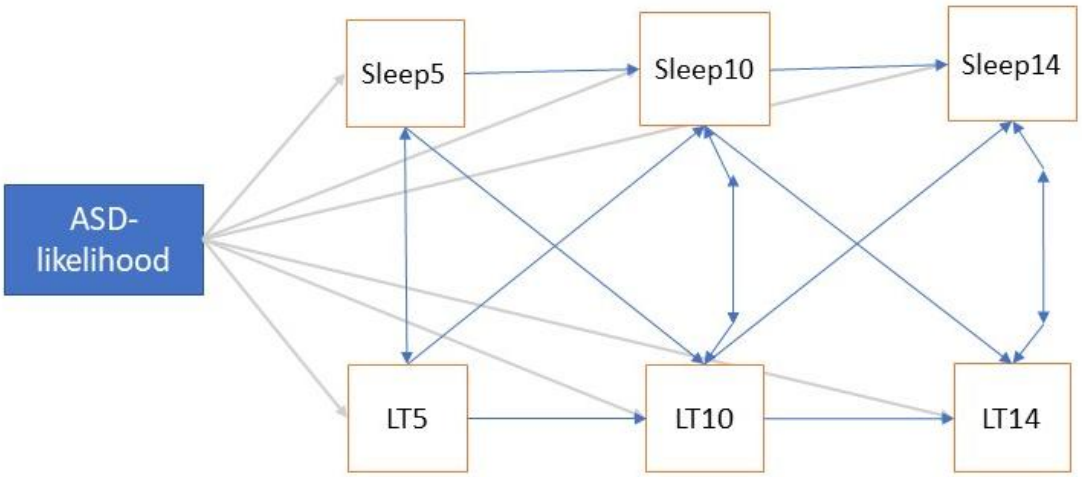

Figure 3.4 CLPM. Double headed arrows are covariances and single headed arrows regressions. LT=Low Threshold.

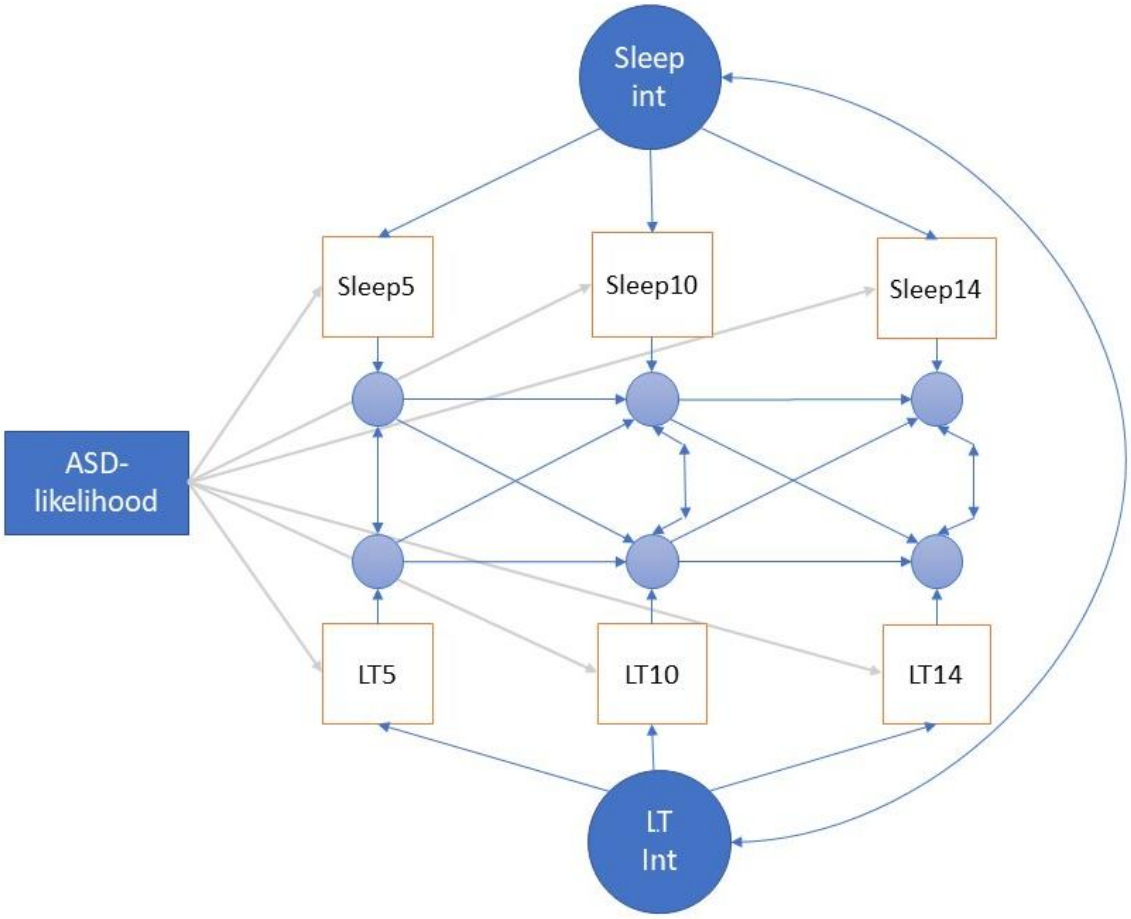

Figure 3.5 RI-CLPM. Latent variables are circles and observed variables are squared. Double headed arrows are covariances and single headed arrows regressions. LT=Low Threshold.

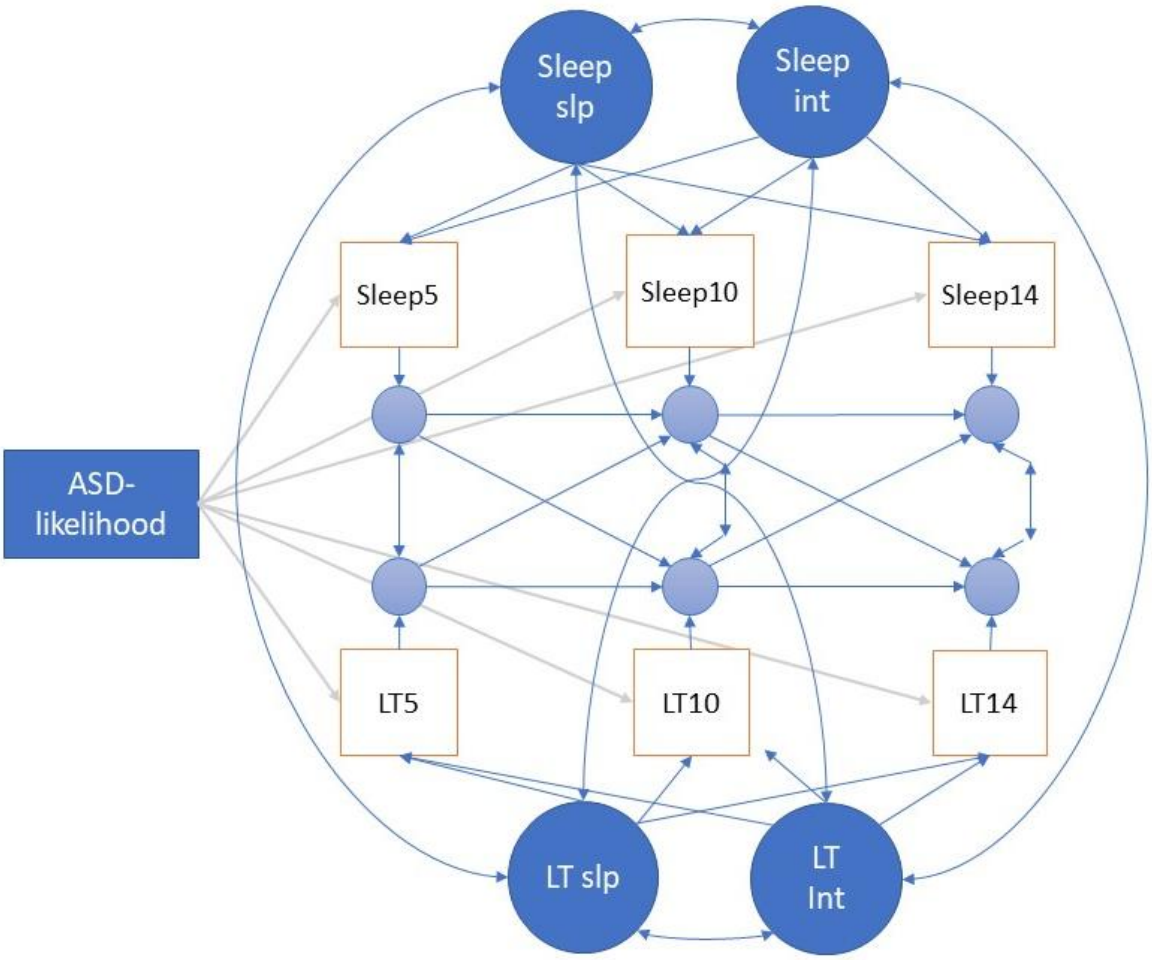

Figure 3.6 LCM-SR. Latent variables are circles and observed variables are squared. Double headed arrows are covariances and single headed arrows regressions. LT=Low Threshold.

3.3 Results

3.3.1 Descriptive statistics

A total of 127 participants contributed data to at least one of the analyses (See table 3.1 for descriptive statistics). The mean age of participants was 177 days (5.8 months) at wave 1, 320 days (10.5 months) at wave 2 and 449 days (14.8 months) at wave 3. Because of attrition, incomplete responses, and additional recruitment at the second and third wave, not all participants had a complete dataset. In figure 3.7 the sample sizes are shown for each variable at each timepoint. The models of awakenings and LT included data of a total of 127 participants of which 64 did not have any missing data. The

models of SOL and LT included data of a total of 127 participants of which 63 did not have any missing data.

Table 3.1 Descriptives of the sample included in the analyses. Means are reported for infants at elevated (EL) and typical (TL) likelihood for autism with standard deviation in brackets. Significant differences between groups are in bold. [a]Chi-square test, [b]independent samples t-test.

	EL	**TL**	**p-value**
N	100	27	
M:F	53:47	17:10	0.48[a]
5 month visit			
Age (in days)	176 (20)	178 (13)	0.52[b]
Awakenings	2.07 (1.45)	2.5 (1.45)	0.21[b]
Sleep onset latency	12.42 (10.35)	11.15 (10.10)	0.60[b]
Low Threshold	1.86 (0.53)	1.79 (0.37)	0.49[b]
10 month visit			
Age (in days)	319 (15)	321 (16)	0.08[b]
Awakenings	2.07 (1.39)	1.32 (1.10)	**0.01**[b]
Sleep onset latency	11.45 (7.51)	7.92 (6.19)	**0.03**[b]
Low Threshold	1.93 (0.65)	1.82 (0.35)	0.32[b]
14 month visit			
Age (in days)	450 (19)	446 (18)	0.33[b]
Awakenings	1.96 (1.49)	1.11 (1.51)	**0.03**[b]
Sleep onset latency	13.18 (11.40)	6.46 (7.25)	**0.002**[b]
Low Threshold	2.02 (0.63)	1.88 (0.35)	0.20[b]

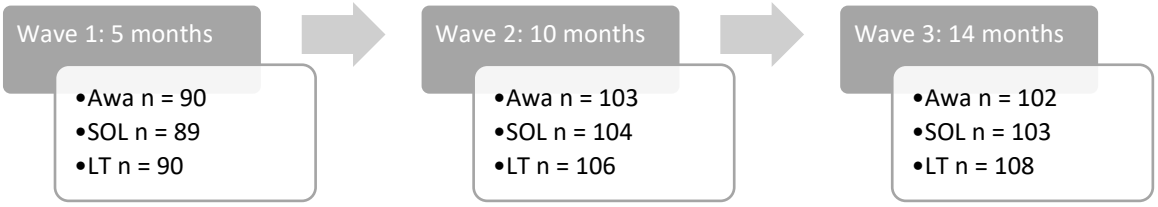

Figure 3.7 Sample size per variable per timepoint. Awa = number of night awakenings, SOL = Sleep Onset Latency, LT = Low Threshold.

Table 3.2 reports the bivariate correlations between the continuous variables used in the longitudinal models. All variables tend to have strong positive correlations over time, assumptions necessary for longitudinal models. From 10 months onwards, night awakenings and sleep onset latency have significant positive concurrent correlations. Also, from 10 months onwards, both sleep measures tend to have positive significant concurrent correlations with LT. Partial correlations (table 3.3) show that early LT tends to have positive associations with later sleep after taking early sleep into account.

However, there is no evidence for the opposite association, with early sleep correlating with later LT after early LT was partialled out.

*Table 3.2 Bivariate correlation table with Spearman correlation coefficients. Mo = months. *p= 0.05-0.01, **p=0.01-0.001, ***p=<0.001*

	Awakenings			Sleep Onset Latency			Low Threshold		
Measure	1	2	3	4	5	6	7	8	9
1. Awa 5 mo	-								
2. Awa 10 mo	0.360**	-							
3. Awa 14 mo	0.388***	0.621***	-						
4. SOL 5 mo	0.191	0.213	0.167	-					
5. SOL 10 mo	0.033	0.371***	0.385***	0.426***	-				
6. SOL 14 mo	0.188	0.303**	0.426***	0.469***	0.631***	-			
7. LT 5 mo	0.110	0.088	0.363**	0.13	0.280*	0.261*	-		
8. LT 10 mo	0.044	0.264**	0.286**	0.245*	0.346***	0.234*	0.614***	-	
9. LT 14 mo	0.162	0.206*	0.310**	0.164	0.283**	0.171	0.542***	0.724***	-

Table 3.3 Partial correlations. Spearman correlations coefficients are reported. Significant correlations are in bold. SOL = Sleep Onset Latency, Awa = Awakenings, LT = Low Threshold.

x	y	covar	n	r	p-value
SOL_5	LT_10	LT_5	77	0.182	0.116
SOL_10	LT_14	LT_10	96	0.06	0.563
SOL_5	LT_14	LT_5	75	0.09	0.444
Awa_5	LT_10	LT_5	78	-0.057	0.624
Awa_10	LT_14	LT_10	96	0.009	0.933
Awa_5	LT_14	LT_5	76	0.103	0.381
LT_5	**SOL_10**	**SOL_5**	**76**	**0.286***	**0.013**
LT_10	SOL_14	SOL_10	94	-0.039	0.709
LT_5	**SOL_14**	**SOL_5**	**73**	**0.27***	**0.022**
LT_5	Awa_10	Awa_5	78	0.051	0.661
LT_10	Awa_14	Awa_10	93	0.147	0.162
LT_5	**Awa_14**	**Awa_5**	**73**	**0.343****	**0.003**

3.3.2 Night Awakenings

The RI-CLPM (a) showed excellent fit on all indices (See table 3.4). The variances of the latent variables representing the trait-like nature of night awakenings and LT were both significant, indicating that there are indeed stable trait-like parts over time for these variables (Unstandardized Est. = 1.14, SE = 0.27, p<0.001; Unstandardized Est. = 0.14, SE = 0.066, p = 0.033, respectively). Additionally, the latent variables are highly correlated (Est. = 0.75, SE = 0.32, p = 0.004), indicating that infants that tend to score higher on LT than their peers, tend to wake up more frequently at night. The autoregressive pathways were not significant except for a positive autoregressive pathway from 10-month LT to 14-month LT (Est. = 0.69, SE = 0.12, p<0.001), showing that a deviation from the expected score on LT at 10 months was carried over in the same direction to 14 months. There was no evidence of reciprocal influences between night awakenings and LT, although there was a marginal negative pathway from awakenings at 10 months to subsequent LT (Est. = -0.47, SE = 0.35, p = 0.073). There were no significant concurrent state-like associations between night awakenings and LT. More (or less) night awakenings than expected, did not coincide with higher (or lower) scores on LT than usual. Autism likelihood status significantly predicted night awakenings at 10 months and marginally at 14 months, such that infants at EL for autism had more night awakenings (Est. = 0.22, SE = 0.08, p = 0.009, Est. = 0.18, SE = 0.10, p = 0.058). All results are summarized in figure 3.8. The LCM-SR, did not converge due to the maximum number of iterations being exceeded. Increasing the number of iterations from 1000 to 5000 did not solve the issue. The LCM-SR was therefore not taken forward. All fit indices of the CLPM, showed poor model fit, therefore the results cannot be reliably interpreted (table 3.4).

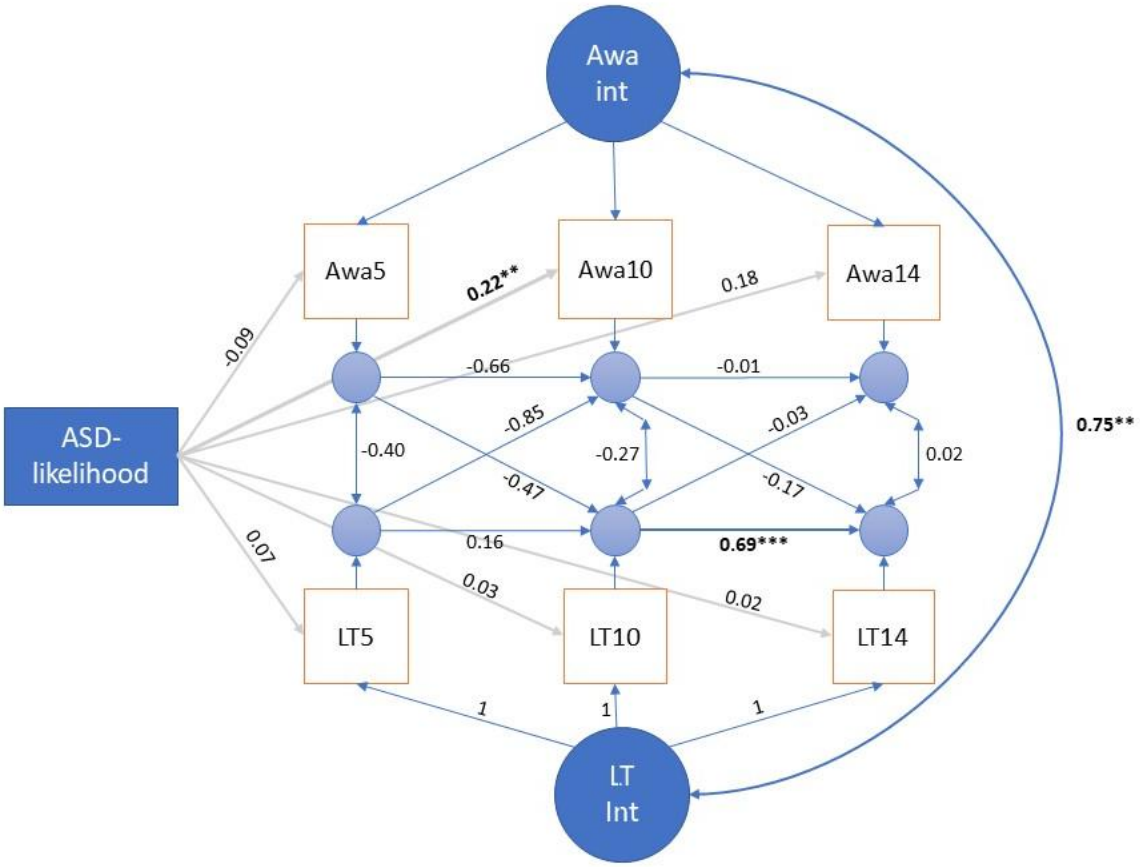

*Figure 3.8 Summary of the results of the unconstrained RI-CLPM. LT= Low Threshold; Awa = Night awakening; int = intercept. *p= 0.05-0.01, **p=0.01-0.001, ***p=<0.001.*

3.3.3 Sleep Onset Latency

None of the models for sleep onset latency showed acceptable model fit (See summary of model fit statistics in table 3.4). RI-CLPMs (a and b) produced negative variance estimates, known as Heywood cases, which are frequently encountered in structural equation modelling. One approach to address Heywood cases is to constrain the variance of the problematic variable to zero or a value close to zero (Dillon et al., 1987). However, setting the residual variance to 0.001 in the RI-CLPMs a and b only caused the Heywood case to jump to other variables. There are a variety of potential reasons why Heywood cases occur, e.g. outliers (Bollen, 1987), small sample sizes (Anderson & Gerbing, 1984), and structural misspecification of the model (Dillon et al., 1987; Kolenikov & Bollen, 2012). Given that the outliers were Winsorized, we opted to reconfigure the model as version c. While the constraining of the cross-lag -, autoregressive - and covariance parameters over time helped eliminate the Heywood cases, the model fit was poor. Also the LCM-SR, produced Heywood cases that could not be resolved by constraining the variance and was therefore not interpreted further. The CLPM equivalent to the best fitting RI-CLPM, resulted in an improper solution as well, with correlations larger than 1, suggesting

misspecification of the model. In summary, none of the models that includes sleep onset latency could be interpreted due to improper solutions or poor model fit.

Table 3.4 Model fit statistics of models of night awakenings (Awa) and Low Threshold (LT) and models of Sleep Onset Latency (SOL) and LT.

Model variables	Model	χ^2 (df)	p-value	AIC	BIC	RMSEA	CFI	TLI	SRMR
Awa	RI-CLPM(a)	0.004 (1)	0.950	1355.53	1446.54	0.000	1.000	1.000	0.001
LT	LCM-SR(a)	No convergence: Number of iterations exceeded (even after 5000)							
	CLPM(a)	30.147 (4)	<.001	1372.51	1454.99	0.227	0.895	0.447	0.067
SOL	RI-CLPM(a)	Warning: negative variance							
LT	RI-CLPM(b)	Warning: negative variance							
	RI-CLPM(c)	30.586 (8)	<.001	2464.50	2535.61	0.149	0.915	0.778	0.128
	LCM-SR(a)	Warning: negative variance							
	CLPM(c)	48.921 (10)	<.001	2473.22	2538.64	0.175	0.854	0.694	0.109

3.4 Discussion

The aim of this study was to evaluate whether sensory processing drives changes in sleep and vice versa, distinguishing for the first time between effects on the within- and between-person level. Only one of the models had acceptable model fit, which was the unconstrained RI-CLPM of night awakenings and LT. That the RI-CLPM yielded better model fit that the traditional CLPM is consistent with previous studies (Griffin et al., 2021; Littlefield et al., 2022; Shi et al., 2023). The results from this RI-CLPM suggest that both night awakenings and LT have trait-like properties in the 5 to 14 month window that was captured in this study. These traits show a strong positive association; infants that, in general, wake up frequently at night, also tend to be more aware and reactive to sensory input. However, this is not reflected in the state-like pathways. If an infant has more awakenings than usual at a specific timepoint, this does not result in higher scores that usual on LT at that time. Neither do higher scores than usual on LT result in a deviation in night awakenings at a subsequent timepoint or vice versa. This study shows no evidence for a reciprocal relationship between sleep and sensory processing in the 5 to 14 month window.

3.4.1 The latent variables

Consistent with literature indicating that infants learn how to sleep through the night in the first years of life (Goodlin-Jones et al., 2001; Henderson et al., 2010), we demonstrated in the Chapter 2 that night awakenings, on average, significantly decrease from 5 to 10 months in the same sample that was used for this study. Nevertheless, we also find a high degree of stability of night awakenings from 5 to

14 months within the same infants. Infants that wake up often at 5 months will likely still wake up often at 10 and 14 months compared to peers. These findings are in line with other studies in infancy using parental report. Hysing et al. (2014) find that frequent night awakenings at 6 months carry over to 18 months. In a similar age range, 8-24 months, night awakenings decrease over time, whilst also showing a high degree of within-person stability (Mäkelä et al., 2018). Also, our measure for sensory processing, LT, exhibited stable properties over the course of this study. E.g. infants that scored high on LT at 5 months consistently scored high at 10 and 14 months. Similarly, longitudinal studies in childhood find that sensory profiles of children with and without autism tend to show high within-person stability over a timespan of years (Baranek et al., 2019; Dwyer et al., 2020; McCormick et al., 2016). The high stability of an infant's sleep and sensory profile, underscores the need to take the trait-like properties into consideration in future studies that are interested in investigating causal relationships between these variables.

The latent factors that measure time-invariant variance, might partly capture the consistent parental accuracy/error in estimating their child's sleep and sensory profile. In other words, the latent factor might partly reflect the caregiver profile, besides the child's actual measurements. Gossé et al. (2022) show that caregivers who are more anxious and stressed rate their child's night awakenings more accurately in concordance with objective measures. Possibly because anxious caregivers are awake more themselves or remember night awakenings better than less anxious caregivers. That caregiver characteristics, such as stress, influence ratings of sleep, has important implications, particularly in samples where such characteristics are highly variable. Caregivers of autistic children experience higher stress-levels than caregivers of typically developing children and children with other developmental delays (Estes et al., 2009; Hayes & Watson, 2013), which could influence the accuracy of the reported measures. Additionally, caregivers of autistic children tend to have heightened sensory profiles themselves (Glod et al., 2017), which may influence their report of sleep and the child's sensory profile. In studies that use caregiver report, the confounding effects of caregiver characteristics are another reason for the separation of trait-like and state-like effects. For example, by implementing a RI-CLPM, which will ensure that the consistent differences in caregiver characteristics are accounted for in the trait-like part, as long as these caregiver traits are time-invariant themselves.

The strong positive association between the latent factors for LT and night awakenings indicates that infants that tend to be more aware and reactive to sensory input, also tend to wake up more frequently compared to others. One possible explanation may be that common underlying mechanisms drive both night awakenings and sensory differences. In Chapter 2 we explored the notion that disrupted GABA functioning may contribute to the association between sleep onset latency and sensory gating. Likewise, atypical GABAergic circuitry may underly both frequent night awakenings and sensory

difficulties by subjective report (Deliens & Peigneux, 2019). GABA is the main inhibitory neurotransmitter in the central nervous system and has an important role in the regulation of the sleep-wake cycle (Oishi et al., 2023). Decreased GABA levels have also been linked to abnormal tactile processing in autistic children (Puts et al., 2017). A recent paper found a marginal association between genetic variation in GABA genes and sensory profiles, in adolescents and adults with and without autism (Hollestein et al., 2023). Interestingly, this association was specific to sensory profiles, but not autism severity scores, confirming a particular role of GABA in sensory related features of autism. More generally, an Excitation/Inhibition (E/I) imbalance has been suggested as a factor in the aetiology of autism (Lee et al., 2017). It is possible that variation in the E/I balance, is partly responsible for both sleep and sensory issues in autistic and non-autistic individuals.

Another mechanism, which could drive both traits is impaired thalamic functioning. This mechanism could be intertwined with an E/I imbalance, because the thalamus contains major inhibitory structures, such as the thalamic reticular nucleus (Guillery et al., 1998). The thalamus is considered the relay station of the brain, filtering information from the outside world. Selective regulation of the stream of sensory input from the periphery to the cortex is important for sleep and processes during wake, such as attention regulation (Z. Chen et al., 2016). Altered thalamic functioning and thalamocortical pathways have been detected in autism, and it contributes to sensory atypicalities associated with autism(S. A. Green et al., 2017; Linke et al., 2018). In relation to sleep, overconnectivity of the thalamus and auditory cortex was associated with sleep onset latency in autistic children (Linke et al., 2021). Possibly, GABAergic functioning in the thalamus is of particular importance. One study found that increased sensory over-responsivity was related to reduced thalamic GABA (Wood et al., 2021). Common underlying mechanisms, such as E/I imbalance and or thalamic functioning may partly explain the association between sleep and sensory issues as trait-like features across life.

In addition, the strong association between the latent factors of LT and night awakenings could partly be explained by time-invariant confounders such as consistent tendencies in caregiver report on both measures, a caregiver that is more attuned to their infant might report more night awakenings as well as pick up more on responsivity to sensory input by the child (Priddis, 2009)

3.4.2 The within-person reciprocal effects

The partial correlations show that high scores on early LT associate with later night awakenings after controlling for early sleep, but not the opposite way around. At a first glance this seems to suggest that there could be a directional effect of sensory processing on sleep, similar to findings from Mazurek et al. (2015) and Manelis-Baram et al. (2021). However, the within- and between-person effects are conflated in the partial correlations, which makes it impossible to know if state- or trait-like differences

are driving the effect. Once between-person effects are accounted for in the RI-CLPM, no significant causal pathways between night awakenings and LT were found over the course of this study. These results imply that strategies to improve sleep or sensory profiles at 5 or 10 months are unlikely to have knock-on effects on sensory profiles or sleep respectively 4-5 months later. Accounting for the trait-like stability via the RI-CLPM shows that the results from the partial correlations are likely driven by between- rather than within-person variance. This demonstrates the importance of incorporating time-invariant traits, as not doing so may result in false conclusions or at the least uncertainties about causal patterns.

Hamaker (2023) highlights the importance of ensuring that the study design and the research questions are well matched in RI-CLPMs. In the next part, I will discuss how this particular study design guides and limits the interpretation of the results. Firstly, the *timeframe* of the study in relation to the development of sleep and sensory systems will be considered. Secondly, the *timescale* of the study, particularly the spacing of the measurements and the expected scale that interactions between sleep and sensory processing operate on will be touched upon.

3.4.3. The timeframe

One major strength of this study is that it captures sleep and sensory issues during an important developmental window. To our knowledge, this is the first longitudinal study to look at sensory processing and sleep in the first year of life. Chapter 2 showed that between 5 and 10 months differences in sleep start to emerge between infants at TL and EL for autism, based on caregiver report. However, it is possible that a causal pathway is established even earlier than 5 months. It is known that sensory neurodevelopment predominantly happens early in life, prenatally and postnatally (Grubb & Thompson, 2004; Whitehead et al., 2018). It is plausible that early sleep contributes to the formation of the sensory circuitry largely before 5 months of age, the earliest measurement in this study. Indeed, evidence suggests a special role of neonatal sleep in sensory neurodevelopment, where state-dependent modulation of sensory activity plays a key role in shaping the sensory circuitry in early infancy. For example, self-generated sensory input is differentially processed during sleep and wake in infant rats (Dooley et al., 2019; Tiriac et al., 2014). During REM sleep, myoclonic twitches, which are isolated muscle movements, activate the sensorimotor cortex. Whereas during wake, activation of cortical sensorimotor neurons from self-generated muscle movements are inhibited. Blumberg et al. (2013) suggest that these twitches during REM sleep have a special role in the development of somatotopic maps of the body, which would benefit from being formed against a background of muscle atonia during sleep. However, this state-dependent modulation of sensory input is transient and specific to a short developmental time-window. It is challenging to measure in humans when that window closes. In rats, adult-like sensory processing that is independent of state, appears from P11-

P13. Rats only start weaning from P21, comparable to 6 months of age in humans (Sengupta, 2013). However, we do know that human infants show a shift from immature to mature EEG patterns around 2-3 months of age (Dereymaeker et al., 2017), and abrupt changes in sensory evoked responses even before birth (Colonnese et al., 2010; Fabrizi et al., 2011).

In line with this, studies in different species, such as prairie voles, mice and fruit flies show that early life sleep disruption has effects on later development, including sensorimotor area development and nociceptive sensitivity (Araujo et al., 2018; Jones et al., 2019, 2021; Kayser et al., 2014; J. S. Lord et al., 2022). Lord et al. (2022) additionally show that effects of early life sleep disruption are more severe in mice with a genetic vulnerability for autism. Interestingly, the timing of the sleep disruptions matter. Early life sleep disruptions in mice (P14-P21), impairs sensory motor gating later in life, but sleep disruption in the adolescent period does not have the same effect. Suggesting a particular vulnerability to sleep disruption early in life (Jones et al., 2019). Again, it is difficult to pinpoint when exactly the equivalent periods are for human infants. It is plausible however that this 'vulnerable' period, occurs before 5 months in humans. As described in Chapter 1 section 1.2, the first months of human life have a distinct sleep pattern and are characterized by a predominance of REM sleep over NREM sleep (Jenni et al., 2004; Roffwarg et al., 1966). Indeed, REM sleep during infancy has been associated with the development of the central nervous system (Knoop et al., 2021). Therefore, disrupted early sleep, before the first measurement of this study, may impair the formation of the sensory circuitry, which would in turn lead to behavioural sensory differences. If these causal mechanisms occur earlier than 5 months, it could explain why LT and night awakenings do not show any significant reciprocal pathways, but rather associated trait-like factors over the course of this study.

It is also possible that disrupted early sleep impacts the formation of the thalamus and thalamo-cortical projections. Impaired thalamic functioning would impact both the expression of mature sleep rhythms as well as sensory atypicalities (Murata & Colonnese, 2019). In this scenario, early sleep disruption results in an underlying mechanism, thalamic impairment, that drives both sleep and sensory differences later in life. This could explain why both traits are highly associated in our dataset from 5 months onwards.

3.4.4 The timescale

Hamaker (2023) illustrates how the design of the study, and in particular the timescale, influences the meaning of the trait- and state-like factors. She demonstrates that the interpretation of the factors very much depends on whether the timescale of the study is on a micro-, meso- or macro-level or across the whole lifespan (Fig. 3.9). What may be constant across days, may be partly fluctuating over weeks. Suppose that measurements are taken every day for a week and a person sleeps badly every

day that week. The stable factor across those seven days will capture that 'poor sleep', because sleep was consistently poor. However, if measurements are taken weekly rather than daily, the meaning of the stable factor will be different. If the person sleeps poorly the first week, but the next weeks they sleep better, then that 'poor sleep' will not be taken up in the stable factors anymore. Instead, it will be a state-specific fluctuation in the model. This illustrates that the interpretation of the trait and state-like factors depend on the timescale of the study, and it is important to consider on which level variation in the construct of interest is theoretically most meaningful.

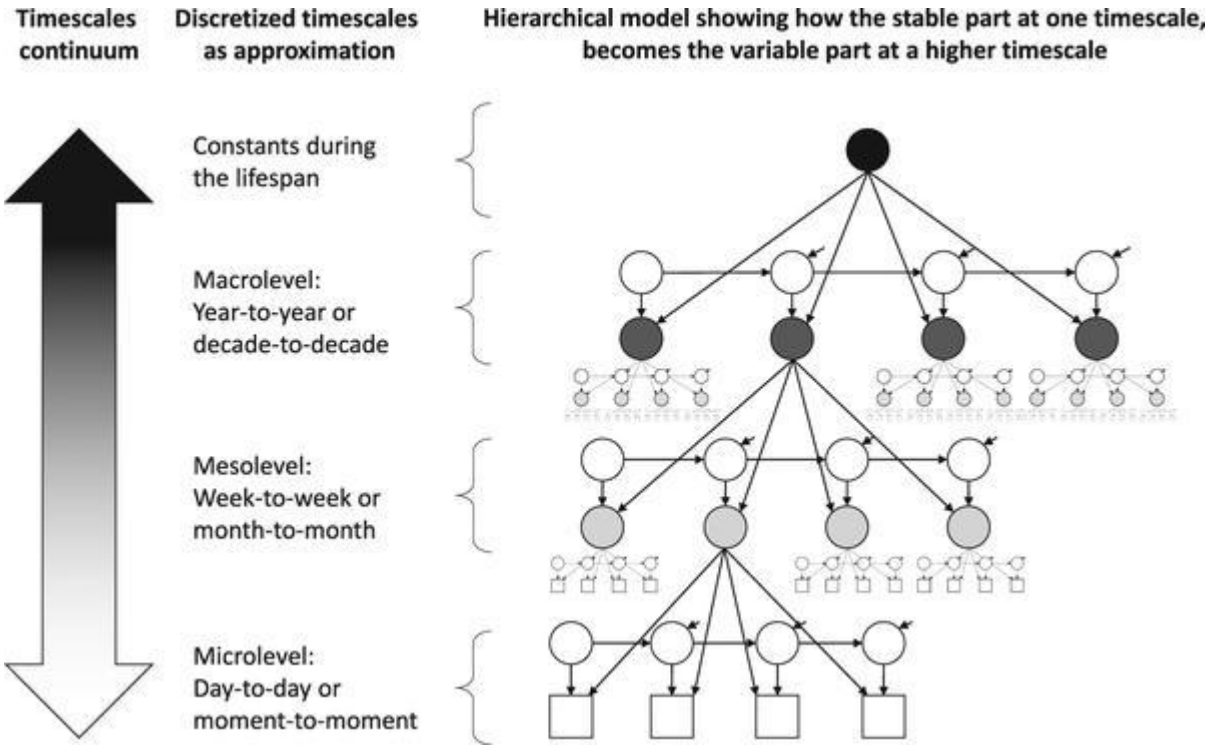

Figure 3.9 The timescales continuum. Figure from Hamaker (2023).

Accumulating effects on a meso-scale

We can imagine that the relationship between sleep and sensory processing manifests differently on multiple timescales. E.g. The effect of one day of bad sleep on sensory processing may be different from the effects of multiple weeks, months or years of bad sleep. This study looked at the reciprocal pathways between sleep and sensory processing over several months, targeting cascading effects. The changes in sleep that manifest over the course of months in infancy are processes such as the development of circadian rhythmicity, sleep patterns and sleep habits. These processes could, at least theoretically, be influenced by sensory atypicalities. E.g. increased reactivity to sensory input could interfere with the development of self-settling strategies that start to appear in the second half of the first year of life (Goodlin-Jones et al., 2001). (Self-)soothing strategies often encompass some sensory component, e.g. touch in stroking or sucking (Uvnäs-Moberg & Handlin, 2015). As outlined above, sleep disruptions could interfere with the proper development of sensory systems, also a process

which likely spans over months. However, in this study, we did not find any evidence of reciprocal effects between 5 and 14 months.

Other studies that use longitudinal panel data tend to use much longer intervals between measurements than months, often years. For example, a study that also used a RI-CLPM, found significant bidirectional reciprocal effects in adults between sleep and pain (Griffin et al 2022). The distance between the measurements was 2 years, showing that state-like differences in sleep can have an influence on variables far into the future. However, the study was looking at older adults, while the current study is focussed on a developmental window where changes in sleep are expected to happen faster. Yet another study, utilising a RI-CLPM, looking at sleep and anxiety, found unidirectional within-person effects from early sleep to later anxiety (Narmandakh et al., 2020). The distance between waves was 2-3 years in this study and was in an adolescent sample of 11- to 21-year-olds, an age range when sleep undergoes developmental changes. It is possible that noticeable differences in sleep and sensory processes manifest over longer timescales, but it is difficult to make a direct comparison to the current study due to the different age ranges and variables used. There are no studies in infancy with a similar design to base the timescale on.

From a more theoretical perspective, the pace of changes in sleep patterns in infancy is much quicker than years (Burnham et al., 2002), and meaningful fluctuations may be captured better with measurements taken every couple of months, starting soon after birth. What the best timescale is to capture meaningful differences in sensory profiles is less straightforward. To our knowledge, no studies have looked at individual trajectories of sensory profiles in infancy. The ITSP itself does not specify the timeframe that caregivers are supposed to keep in mind when answering questions about their child's behaviour. We assume that caregivers take a sort of 'average' of their child's behaviour, but it is impossible to know how far back they go when rating the frequency of behaviours.

Immediate effects on a micro-scale

In addition to a timescale of months, sleep and sensory processing may influence each other on a day-to-day basis, where poor sleep increases next day sensory issues and heightened sensory sensitivity worsens sleep that day (Gumenyuk et al., 2013; Zhang et al., 2019). The current study did not test this hypothesis. However, further studies could consider a few approaches to test whether there is a causal link between sleep and sensory processing on a day-to-day scale.

One approach involves conducting a longitudinal study, but on a micro-scale, measuring sensory processing and sleep each day. Recently there has been an increase in studies in psychology that model within-person processes using intensive longitudinal designs, that use many repeated measures, spaced densely in time (Hamaker & Wichers, 2017). In sleep research, for example, Chevance et al.

(2022) found meaningful within-person day-to-day fluctuations in sleep in correspondence to physical activity. Both variables were measured for more than 100 days.

Another approach could be to conduct an intervention study, to alleviate either sleep or sensory problems. Studies assessing the effectiveness of sensory interventions on sleep do hint at causal effects on shorter timescales. For instance, autistic adults reported improved sleep quality when using weighted blankets (L. Green et al., 2020) and interventions based on massage before bedtime also showed improvements in parent reported sleep measures (Silva et al., 2007; Spira, 2021).

Lastly, an experimental design could measure the effects of sensory input on sleep in individuals with different sensory profiles. To our knowledge, only one study in non-autistic adults has looked at the effect of sensory input on sleep in relation to an individual's sensory profile (Lechat et al., 2021). This study revealed that individuals that report high subjective sensory sensitivity show differences in EEG markers during sleep in response to stimulation. In the next chapters we will use an experimental design to test the effect of sensory input on sleep in infants with a range of sensory profiles.

3.5 Conclusion

In this study we do not find any evidence for cascading effects of early sensory processing difficulties on night awakenings between 5 and 14 months or vice versa. The strong correlation between the latent factors and lack of cross-lagged effects implies that, at least in this time window, neither early sleep nor early sensory processing drives the other, but rather that a common mechanism underlies both. This has implications for interventions targeting sleep or sensory issues, as it implies that improving sensory symptoms will not affect sleep patterns over the next months or vice versa. However, this study focussed on cascading effects over the course of months and it is possible that interventions will improve sleep or sensory issues on a more immediate time scale, e.g. the next day or week. It is also possible that causal pathways are established earlier than the start of this study. Future work should capture sleep and sensory profiles as early as possible. Common biological mechanisms that could potentially drive both sensory and sleep difficulties are disrupted thalamic and/or GABAergic functioning. However, commonalities between the measures could also reflect consistent tendencies of caregiver report. The use of objective measures would help clarify to what extent the caregiver's profile drives the association between sleep and sensory processes. From a methodological standpoint, this study contributes to emerging literature that underscores the importance of accounting for time-invariant stability of measurements. In Chapter 5 immediate effects of sensory profiles on sleep will be explored using an experimental design incorporating objective measures of sleep.

Chapter 4.
Adapting methods for developmental populations

4.1 Introduction

The visual detection of transient events, such as sleep spindles and K-complexes, by experts has long been considered the gold standard in the sleep field. However, this is a demanding and time-consuming task. Although there are general guidelines that define sleep spindles or K-complexes, the reliability of expert scorers is far from perfect, with large variation between experts and even within the same scorer when re-scoring the same segment (Wendt et al., 2015). There are several approaches to address the low reliability problem. One option is for multiple experts to score the same data and use qualitative confidence scores. From these scores, weighted means can be calculated to make up the final count. While this may improve accuracy, it is time- and resource-intensive. Alternatively, automated detection methods can be used, which are efficient and objective. Moreover, algorithms consistently produce the same results, no matter how many times it is given the same data, thereby eliminating the within-scorer variability. However, a major limitation of automated detection methods is that they perform worse than human experts - and even non-experts - when presented with slightly atypical data (Warby et al., 2014).

In recent decades, interest in automated detection methods for sleep micro-events such as sleep spindles, slow waves and K-complexes has grown exponentially. New and improved detection algorithms for adult data seem to be developed almost daily (Tapia-Rivas et al., 2024). However, there has been a growing awareness of the reduced performance of these algorithms in special populations, such as individuals with medical conditions that affect EEG signals, as well as elderly and infants. Recently, efforts have been made to address these challenges, leading to the development of specialized detection algorithms (L. Wei et al., 2022). A particular challenge for developmental research is that features of micro-events change rapidly with age, especially in the first year of life (see Chapter 1 section 1.2, and section 4.2.2 and 4.3.2 below). For example, an algorithm that is trained on data of 3-month-olds might not perform optimally anymore in 6 month-olds.

The aim of this chapter is to outline the methodological approach to detect sleep spindles and K-complexes in a 8-11 month-old cohort. This cohort is part of the SNOOSE study, which is discussed in detail in Chapter 5. Sleep spindles and K -complexes are addressed separately. For both, current approaches to detect events will be outlined, focusing on infancy where possible. Then, developmental changes in features of sleep spindles and K-complexes in the first year of life will be discussed. The challenges that these developmental changes pose for detection with automated methods will be outlined throughout. Lastly, for sleep spindles, I present adaptations to an existing algorithm, YASA, to improve performance in 8-11 month-olds. For K-complexes, the automated detection of *evoked* K-complexes is trialled.

4.2 Sleep spindles

4.2.1 Approaches to detect sleep spindles in infancy

Studies investigating sleep spindles in the first year of life implement a variety of methods. Some studies do not distinguish sleep spindles as distinct events, but measure sigma activity as a proxy (Kärki et al., 2022; Satomaa et al., 2020). Sigma activity or power is the squared amplitude of oscillations in the sigma range, usually anywhere between 7-16 Hz. This approach involves analysing the overall sigma power of the signal, but does not isolate individual spindle events. To detect spindle events, either visual (Ventura et al., 2022) or automated detection is used (D'Atri et al., 2018; Friedrich et al., 2015; Jaramillo et al., 2023; Sokoloff et al., 2021).

The majority of studies use an automated method that tends to follow the same general key steps:

1. **Bandpass Filtering:** The data is filtered within the sigma range, typically anywhere between 7 and 16 Hz.

2. **Root Mean Square (RMS) representation**: The filtered signal is then transformed into an RMS representation, which provides a measure of the signal's power or amplitude over time. Usually, the signal is segmented in windows of 1 or 0.5 seconds, and the averaged squared power or amplitude over that time window is calculated.

3. **Thresholding**: The RMS of each segment is compared against specific thresholds to identify potential spindle events. For example, a segment might be classified as a spindle if its RMS value exceeds 1.5 standard deviations from the mean for a duration of 0.5 to 2 seconds (Vallat & Walker, 2021).

While this is the general workflow, each team sets different threshold and uses customized algorithms that have slight variations. For example, Friedrich et al. (2015) use a customized algorithm that first determines the sigma peak frequency for each individual participant. They then apply a more narrowly defined bandpass filter, set at ±1.5 Hz around each individual's sigma peak. Recently, an algorithm was developed for infant data specifically (L. Wei et al., 2022) which was trained and validated on the nap data of 4-month-olds. Their algorithm was trained on data of 81 infants using a random forest algorithm and tested on 30 infants of the same age. Although their trained algorithm performed well within this dataset, it has yet to be evaluated on other age groups or datasets that use different EEG systems.

4.2.2 Development of sleep spindles

The first sleep spindles typically emerge between 6-weeks and 3-months of age (Ellingson & Peters, 1980; Louis et al., 1992), although at this stage, they are not fully developed yet. In Chapter 1 section

2.3, I provided a brief overview of the development of sleep spindle characteristics and topography in the first year of life. These developmental changes may affect sleep spindle detection visually and automatically. Many automated detection methods are feature-based, meaning that particular spindle characteristics are identified by experts and used as inputs for a model or algorithm. A few of those features are particularly influential for accurate automated detection: Sleep spindle amplitude or power, duration and frequency. Next, I will describe what is currently known about the developmental trajectories of these features in the first year of life and how they might affect the detection of sleep spindles.

As discussed earlier in Chapter 1, sleep spindle **duration** undergoes large changes across the first year of life. In the first few months when sleep spindles emerge, the length of sleep spindles tends to be the longest they will ever be. A clear decrease in duration can be seen after 5 months (see Fig 4.1). Ventura et al., who detected sleep spindles visually in 91 nap recordings of 4-5 month-olds, found that sleep spindles were 2.9 seconds long on average. In adults, sleep spindles tend to be between 1 and 2 seconds on average (2020). This has implications for threshold settings of sleep spindle duration for automated methods. Although a 4 second long sigma oscillation may likely be noise in an adult sleep recording, it may be a true spindle event in a 4 month-old's data. This suggests that an algorithm's threshold for sleep spindle duration should be adapted depending on age range.

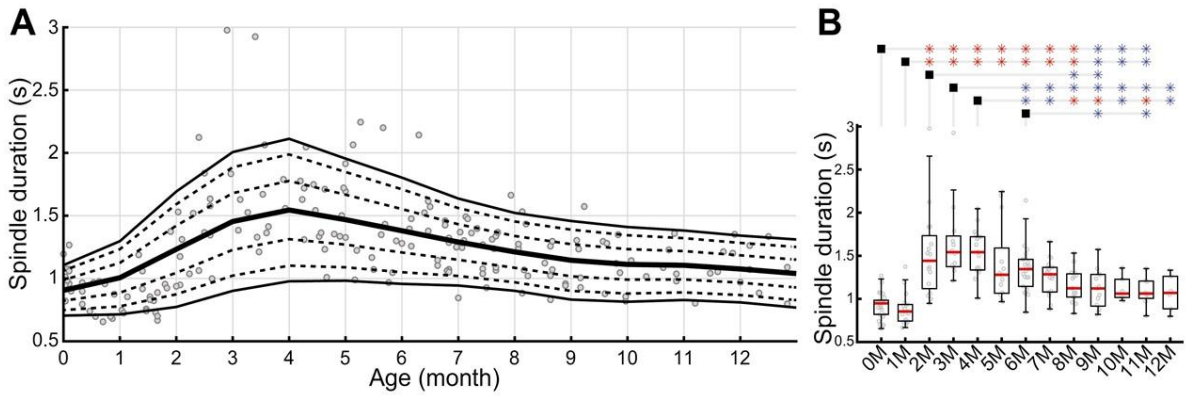

Figure 4.1 Development of sleep spindle duration across the first year of life. A. Smooth trajectory. B. Box-plots per month. Figure from Kwon et al. (2023).

To our knowledge, only one study has looked in detail at the development of sleep spindle **amplitude** across the first year of life. This longitudinal study looked at 1.5 to 6 months and showed a significant increase in sleep spindle amplitude (Louis et al., 1992). Sigma power during NREM sleep, which is highly correlated with mean spindle amplitude (Purcell et al., 2017), has been studied more often. For example, a longitudinal study in early childhood found that sigma power during NREM sleep increases from 2 to 5 years old (McClain et al., 2016). Although they did not include any timepoints before 2

years, the findings suggest that sleep spindle amplitude may be lower in early childhood and infancy. Indeed, a study from D'Atri et al. (2018) shows a clear visual increase in spindle amplitude from 0 to 4 years old (see Fig. 4.2), but unfortunately they did not quantify sleep spindle amplitude or power in their study.

As described in Chapter 1, the power of oscillations changes depending on sleep pressure. E.g. SWA decreases over the course of the night (Dijk et al., 1987, 1990; Esser et al., 2007; Pappenheimer et al., 1975), reflecting a decrease in homeostatic sleep pressure the more a sleeper sleeps. Interestingly, a study in 4-5 month-old infants found that sleep spindle power decreases in response to diminished sleep pressure from one NREM cycle to the next (Ventura et al., 2022). In adults, the opposite is observed: When sleep pressure decreases, sigma power increases (Werth et al., 1997). Lower amplitudes could significantly affect the detection of true sleep spindles. Indeed, Purcell et al. (2017) show through computational modelling that accuracy of sleep spindle density estimates is dependent on sleep spindle amplitude. This indicates that perhaps sensitivity thresholds need to be lower when measuring sleep spindles in infancy.

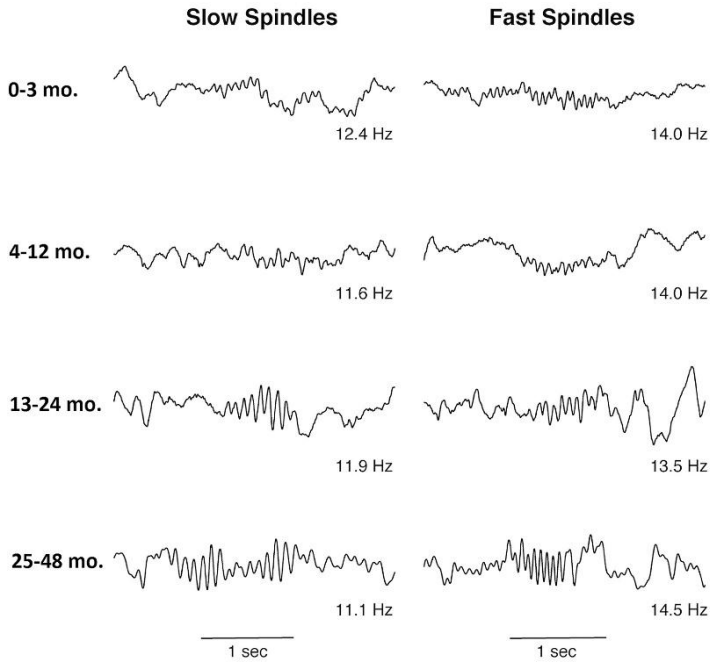

Figure 4.2 Representative examples of sleep spindles in different age groups. Figure from D'Atri et al. (2018).

Sleep spindle **frequency** is around 13 Hz in the first year of life, both for sleep spindles measured in frontal and central channels (Kwon et al., 2023; Ventura et al., 2022). Between the first and second year of life, slower spindles start to appear in the frontal channels (see Fig. 4.3). D'Atri et al. propose that these slower spindles are the first mature spindles, whilst the earlier spindles that peak at 13 Hz are an immature antecedent. Although this may have implications for the functional significance of

sleep spindles, it likely does not impact standard automated detection. This is because the 13 Hz frequency falls within the standard sigma ranges typically used for spindle detection (9-16 Hz). However, it does imply that it is unnecessary to detect slow and fast spindles separately in the first year of life.

Next, I will describe how I used this information to adapt an existing algorithm to detect sleep spindles in the SNOOSE cohort.

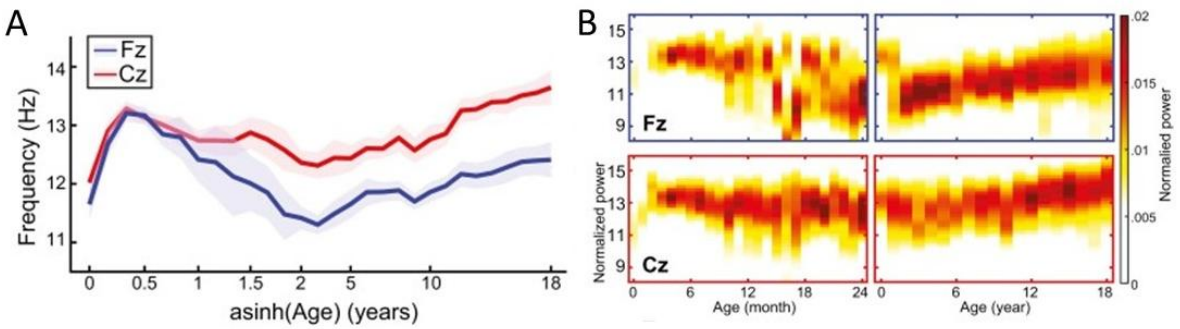

Figure 4.3 Sleep spindle frequency across development. A. Changes in mean frequencies of spindles detected in Fz and Cz. B. Power changes per frequency in Fz and Cz. Figure adapted from Kwon et al. (2023).

4.2.3 Sleep spindle detection in the SNOOSE study

4.2.3.1 Rationale

While some customized algorithms for sleep spindle detection are freely available, their underlying code often remains inaccessible which limits their adaptability. For example, the specialized infant algorithm developed by Wei et al.(2022) for 4 month-olds is available online for public use but cannot be modified. This lack of flexibility can be a significant limitation when data is used that does not match the conditions of the original training dataset exactly.

Given these limitations, we opted to use an existing sleep spindle detection algorithm that offers greater flexibility. Yet Another Spindle Algorithm (YASA) is an open source software for sleep research written in Python (Vallat & Walker, 2021). One of the features of YASA is an automated spindle detection function which has parameters and thresholds that can easily be adjusted. The default settings of YASA are based on sleep recordings of 2 to 80 year-olds, which does not include the age range of the SNOOSE study. Therefore, we decided to adjust the default thresholds by cycling through an array of thresholds to determine which ones are most in agreement with visual detection. This approach follows a common principle for algorithm validation. First, parameters are optimized based on a training dataset to maximize agreement with a ground truth – here the manually annotated sleep spindles. Performance is evaluated based on precision, recall and F1-scores (explained in detail in

4.2.3.2.4). The adjusted algorithm is then tested on a separate validation dataset and should perform similarly to the training dataset.

4.2.3.2 Methods

4.2.3.2.1 Sample

Data used in this chapter is part of the SNOOSE study, which is described in detail in Chapter 5. In short, infants at EL and TL for autism were invited to the sleep lab at the university of East Anglia twice to take a nap. At one visit, infants slept undisturbed (Baseline condition). At the other visit, auditory stimulation was playing during the infant's nap (Stimulation condition). The order of visits was counterbalanced. All infants were between 8 and 11 months old. At the time of the analysis, data from 69 naps had been recorded. However, a few additional infants were included afterwards and are part of the analysis in Chapter 5. Out of 69 recordings, 11 were excluded from the analysis: five due to noise in the C4 channel and six due to noise in one of the reference channels. Therefore, a total of 58 recordings are used for these analyses. To create training and validation datasets, 29 recordings were randomly chosen using the pd.sample() function in python to use as the training set. The remaining 29 recordings were used as the validation set. The training and validation set were balanced in terms of sex, autism-likelihood status, nap condition (baseline or stimulation), and order of visit (see table 4.1).

Table 4.1 Comparison between the training and validation datasets. EL = Elevated Likelihood for autism; TL = Typical Likelihood for autism.

	Training	*Validation*	*Chi-Squared*	*p-value*
N	29	29		
Male : Female	16:13	15:14	0	1
EL : TL	4:25	5:24	0	1
Baseline : Stimulation	12:17	16:13	.621	0.431
Visit 1 : Visit 2	16:13	16:13	0	1

4.2.3.2.2. Preprocessing

Preprocessing steps are described in detail in Chapter 5. In short, the data was re-referenced to the linked mastoids. Automatic artefact rejection was performed in all sleep stages using the artefact rejection function from YASA with a 1 second window. Both automatic and visual sleep spindle detection were performed on artefact-free N2 and N3 epochs.

4.2.3.2.3. Automatic detection

In YASA, an event is classified as a sleep spindle depending on several adjustable parameters, which we modified based on previous infant literature. The default sleep spindle duration in YASA is set to 0.5-2 seconds. In the SNOOSE age range (8-11 months), sleep spindle duration should already be decreasing, but some infants may still have longer sleep spindles than adults. To account for this variation, the upper limit was increased to 4 seconds. YASA also defines the minimum distance between sleep spindles. At default, sleep spindles that are closer than 500 ms are merged into a single sleep spindle. Given that infant sleep spindles often have lower amplitudes, longer durations, and do not have their typical waxing and waning shape, there is a higher likelihood of spindles being mistakenly split into two separate events. We therefore increased the minimum distance slightly to 750 ms to ensure one sleep spindle was not mislabelled as two. The default frequency range settings in YASA are 12-15 Hz. We opted for a wider frequency range to maximize the inclusion of sleep spindles (Coppieters 't Wallant et al., 2016; J. Cox et al., 2016).

The YASA algorithm detects spindles based on three additional thresholds: Root mean square (RMS), Relative power and correlation. The first threshold is the moving **Root Mean Square (RMS)** of the EEG signal within the sigma band. It detects an increase in sigma power in the signal. In the default setting the RMS threshold is set to 1.5, which means the power in the sigma band needs to exceed the mean sigma power plus 1.5 times the standard deviation. The second threshold, the **moving correlation,** calculates the Pearson correlation between the raw, unfiltered EEG signal and the EEG signal filtered in the sigma band. The purpose of this threshold is to detect spindles that are clearly visible even in the raw EEG signal. In the default setting the Pearson correlation coefficient needs to exceed 0.65. Lastly, the third threshold, the **relative power** refers to the proportion of the sigma power in the signal's total power. The default setting is 0.2, meaning that at least 20% of the signal's total power must be in the sigma band for an event to be classified as a spindle. It is recommend to lower this threshold when detecting spindles in N3, a sleep stage with high power in the lower frequency ranges. This may be particularly relevant for infants as they tend to have large amplitude background activity, and, as mentioned above, the spindle power tends to be lower. For more information on these thresholds see the YASA website. These three thresholds largely determine the sensitivity of the detection algorithm. We systematically adjusted these thresholds to optimize the algorithm performance on this particular dataset, which is described below.

4.2.3.2.4. Performance evaluation

As a ground truth, sleep spindles were visually identified in artefact-free N2 and N3 in channel C4, using the *Sleep* software (Combrisson et al., 2017) by annotating the start and end time of each sleep spindle. Ten initial recordings were scored by two independent scorers (ADL and MW) and compared

until agreement was reached. The remaining recordings were scored by one scorer (MW). Automated detection was run with varying thresholds and the outcomes were compared to the visual detection results.

In a *first round*, 10 'exploratory' algorithms with varying thresholds were run. The thresholds were lowered systematically by 10% increments from the default algorithm (see table 4.2), this makes the thresholds more lenient. The minimum thresholds were set at 10% because at least one threshold should be greater than zero for the algorithm to work. During this phase, all three thresholds were lowered equally. The purpose of the initial step was to identify a broad range for further systematic exploration in *round two*, where each threshold could be varied independently to fine-tune the algorithm's performance. All three thresholds were varied, because we did not have a strong a priori reason to prioritize one threshold over the others.

Table 4.2 Thresholds of the 10 algorithms that were run in the initial exploratory phase.

Algorithm	RMS	Correlation	Relative power
1: Default	1.5	0.65	0.2
2: 90%	1.35	0.585	0.18
3: 80%	1.2	0.52	0.16
4: 70%	1.05	0.455	0.14
5: 60%	0.9	0.39	0.12
6: 50%	0.75	0.325	0.10
7: 40%	0.6	0.26	0.08
8: 30%	0.45	0.196	0.06
9: 20%	0.3	0.13	0.04
10: 10%	0.15	0.065	0.02

The performance of a detection algorithm can be evaluated using several metrics: Recall, Precision and the F1-score (Liu et al., 2017; Warby et al., 2014). These metrics rely on a comparison of the detected events by the algorithm and the ground truth. First, a few key terms need to be explained. A true positive (TP) is a detected spindle that is also identified in the ground truth (the human expert detection). A False Negative (FN) is a spindle present according to the ground truth, but undetected by the algorithm, or in other words, a missed spindle. A False positive (FP) is a spindle detected by the algorithm which is not present in the ground truth scoring.

Recall is the proportion of all true spindles (according to the ground truth) that were correctly detected by the algorithm. It is expressed as:

$$Recall = \frac{TP}{TP + FN}$$

Precision is the proportion of all detected spindles by the algorithm that are true positives. It is expressed as:

$$Precision = \frac{TP}{TP + FP}$$

The *F1-score* is the harmonic mean of recall and precision, providing a single metric that balances both precision and recall. It is expressed as:

$$F1 = \frac{TP}{TP + FP}$$

YASA provides a function to calculate the performance of an algorithm compared to a ground truth, including recall, precision and the F1-score. Whether an estimated spindle is considered a TP is dependent on the temporal overlap between the estimated and expert-detected spindle. In YASA, this can be adjusted by changing the maximum distance between the start of the estimated and expert-detected spindles. The maximum distance was set to 1 second. The average F1-score of all recordings in the training set was calculated to obtain one score per algorithm. The best-performing algorithm was chosen based on the highest average F1-score.

However, precision, recall and F1-scores are dependent on the number of detected spindles. For example one FP will have more weight in a recording with fewer spindles compared to a recording with many sleep spindles. Therefore, we also tested whether the best-performing algorithm showed an improvement compared to the default algorithm in the estimated sleep spindle density (N/min), a measure that controls for the length of the recording. To do so, sleep spindle density (N/min) was calculated for the default algorithm, the best-performing adjusted algorithm and manual detection. Pearson correlations were calculated between sleep spindle density of the default algorithm and the manual detection, and the adjusted algorithm and the manual detection. To test if there was a significant improvement, the two correlations were compared using the Fisher's Z-transformation. Because the correlations are in the same groups and the two correlations are overlapping - due to one shared variable (sleep spindle density from the manual detection) - a test based on dependent groups was used. The test was performed using the function *cocor.dep.groups.overlap* from the R-package *cocor* (Diedenhofen & Musch, 2015). A p-value lower than 0.05 indicates a significant difference between the correlations.

4.2.3.3 Results

Round one

Table 4.3 Performance metrics for the 10 exploratory algorithms. The maximum values per metric are displayed in bold.

	Precision				Recall				F1			
Algorithm	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max
1: Default	**0.84**	0.23	0.00	1.00	0.30	0.19	0.00	1	0.40	0.16	0.00	0.67
2: 90%	0.79	0.17	0.45	1.00	0.42	0.20	0.03	1	0.51	0.15	0.06	0.80
3: 80%	0.72	0.20	0.34	1.00	0.52	0.19	0.03	1	0.56	0.14	0.06	0.80
4: 70%	0.63	0.18	0.25	1.00	0.61	0.18	0.06	1	**0.58**	0.13	0.11	0.78
5: 60%	0.51	0.20	0.17	0.89	0.65	0.15	0.21	1	0.53	0.14	0.27	0.74
6: 50%	0.38	0.19	0.11	0.80	**0.66**	0.13	0.39	1	0.45	0.15	0.19	0.70
7: 40%	0.26	0.15	0.05	0.56	0.63	0.12	0.43	1	0.35	0.16	0.09	0.62
8: 30%	0.16	0.10	0.02	0.35	0.54	0.15	0.23	1	0.23	0.13	0.03	0.45
9: 20%	0.08	0.06	0.00	0.28	0.42	0.17	0.00	1	0.13	0.08	0.00	0.37
10: 10%	0.03	0.03	0.00	0.17	0.22	0.12	0.00	0.5	0.05	0.05	0.00	0.25

The average performance of each algorithm, measured by the precision, recall and F1-score, is displayed in table 4.3. The default thresholds resulted in high precision but low recall scores, meaning that the algorithm missed many true spindles in the recording. As expected, the precision decreased when the thresholds were lowered, ranging from 0.84 (SD = 0.23) for the default parameters to 0.03 (SD = 0.3) for the lowest thresholds, likely due to an increase of false positives. The highest average score for recall (mean = 0.66, SD = 0.13) was obtained when thresholds were lowered by 50%. Lowering the thresholds below 50% did not result in improved recall. The average precision versus recall scores per algorithm are plotted in figure 4A. The highest F1-score (mean=0.58, SD=0.13) was obtained by lowering the thresholds to 70% (algorithm 4). The same algorithm also has the highest R^2 value when its sleep spindle density is regressed on the ground truth sleep spindle density (see Fig. 4.4B).

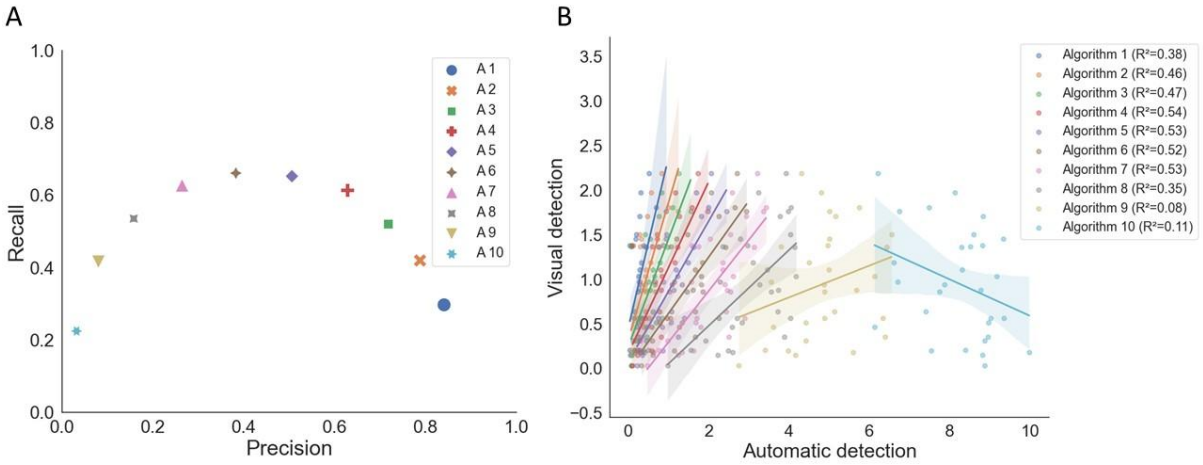

Figure 4.4 Performance of 10 exploratory algorithms with varying thresholds (see table 4.4 for thresholds per algorithm). Algorithm 1 has the default thresholds. A. Average recall and precision values per algorithm. B. Sleep spindle density based on visual detection (Y-axis) compared to sleep spindle densities based on automated detection (X-axis).

Round two

Based on these results we attempted to improve the performance within a range where precision and recall where both acceptable (above 0.5). In this second step, all possible combinations were tested systematically by varying each threshold individually (see table 4.4). The minimum was set to 55% and the maximum to 85% with increments of 5%. For example, the RMS and correlation threshold would be kept on 85% while the relative power threshold would be lowered stepwise in 5% increments. In total, 343 threshold combinations were tested. Results from these analyses showed only minor improvements. The average F1-scores of all different threshold settings ranged from 0.491 to 0.593. The best performing algorithm based on the F1-score had thresholds set to: rms 85% = 1.275, correlation 80%= 0.52 and relative power 65% = 0.13. For this algorithm the average precision was 0.635 (SD=0.174) and the average recall was 0.626 (SD= 0.192).

Table 4.4 Threshold settings for round 2.

Parameter	Min (55%)	Max (85%)	Increment (5%)
RMS	0.825	1.275	0.075
Correlation	0.3575	0.5525	0.0325
Relative Power	0.11	0.17	0.01

In a next step, we used the best performing threshold settings on the validation set, which yielded similar results (see table 4.5). Sleep spindle density from the default algorithm correlated significantly with sleep spindle density obtained from the manual detection ($r = 0.61$, $p < .001$), as did sleep spindle

density from the adjusted algorithm (r = 0.73, p < .001). When comparing the correlations, the correlation with the adjusted algorithm was significantly higher than the correlation with the default algorithm (z = -1.97, p = 0.049), supporting the choice for the adjusted algorithm (see Fig. 4.5).

Table 4.5 Comparison between the performance on the training and validation datasets.

Dataset	Precision				Recall				F1			
	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max
Training	0.635	0.174	0.261	1.000	0.626	0.192	0.061	1.000	0.593	0.139	0.111	0.776
Validation	0.622	0.191	0.000	0.840	0.543	0.236	0.000	1.000	0.553	0.189	0.000	0.800

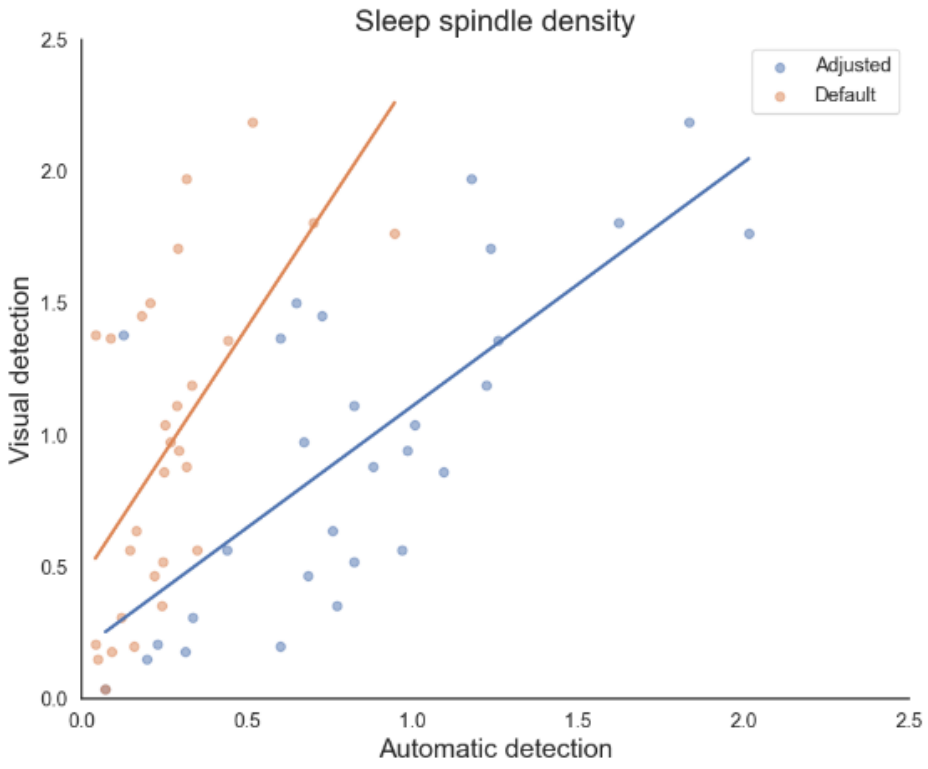

Figure 4.5 Scatterplots with linear regression model fit of sleep spindle density based on visual and automatic detection. In blue is the best performing (based on F1-score) algorithm with adjusted thresholds. In orange is the algorithm with the default threshold setting.

4.2.3.4 Discussion

We aimed to improve the performance of an existing spindle detector, YASA, originally trained on data spanning from early childhood to adulthood, for use in infant sleep recordings, age 8 to 11 months. The YASA algorithm is based on the A7-spindle detector designed by Lacourse et al (2019), which reached an average F1-score of 0.7 in adult sleep recordings. However, when applied to our dataset of 8-11 month-olds, the performance significantly declined, with an F1-score of 0.4. The reduction is

primarily driven by a low recall score, indicating that the algorithm fails to detect a large amount of spindles identified by visual detection. However, the spindles that were identified by the automated detector were largely correct, as reflected by a high precision score.

To improve the algorithm's performance, we used a subset of the data (the training set) to test a range of threshold settings. In a first step, the three detection thresholds were lowered simultaneously in 10% increments to identify a broad range of optimal settings. The algorithm performed best when the thresholds were set between 55% and 85% of the original default values. In a second step, we fine-tuned the algorithm by lowering each threshold individually in 5% increments and tested all possible combinations within the 55% to 85% range. The best performing algorithm on the training set had an F1-score of 0.59 and a similar performance in the validation set with an F1-score of 0.55.

Adjusting the threshold markedly improved the algorithm's performance compared to the default threshold settings, raising the F-score from 0.4 to 0.55. Although this is a significant improvement, the adjusted algorithm is still not as effective as the original A7 algorithm in adults (F1 =0.7). One possible reason for the lower performance is that N3 was included in our analysis. Abrupt increases or decreases in voltages, such as slow waves during N3, impact other frequency bands (Kramer et al., 2008), which may affect sleep spindle detection (Purcell et al., 2017). If the inclusion of N3 is the reason that spindles were underdetected, we would expect worse recall scores in recordings that had a lower proportion of N2 to N3 and better recall scores in recordings with higher proportions of N2 to N3. However, there was no significant correlation between the N2/N3 proportions and recall scores, either using the default settings ($r = -0.15$, $p = 0.43$) or the adjusted settings ($r = -0.24$, $p = 0.20$). This suggests that underdetection of sleep spindles is not due to the inclusion of N3.

When looking at the three thresholds separately, lowering the relative power, which reflects the proportion of the sigma power in the signal's total power, seemed particularly beneficial to enhance the performance. Specifically, the optimal settings of the best performing algorithm were: RMS = 1.276 (85%), correlation = 0.52 (80%) and relative power = 0.13 (65%). That the relative power threshold needed to be lowered in particular may reflect lower amplitudes of sleep spindles in infancy in combination with the high background activity (D'Atri et al., 2018; Frey et al., 2016; McClain et al., 2016). It is possible that the human eye can adapt its 'thresholds' more flexibly to higher background noise than an algorithm.

In comparison to other automated spindle detectors, an F1-score of 0.55 is average – not the worst, but certainly not the best either. For example, Kwon et al. (2023) report an F1-score of 0.48, while the infant-specific algorithm developed by Wei et al. (2022) reaches high F1-scores of around 0.88. The disparity in these scores could be attributed to several factors, including different algorithms and

methodologies used. However, it is possible that the lower performance in Kwon et al.'s study is due to the wide age range used (0-18 years), while Wei et al. trained and tested their algorithm on a very specific dataset with a narrow age range (4-5 months). This highlights the challenge of finding an algorithm that fits all. Ideally, an sleep spindle detector would be developed that has separate thresholds settings depending on the specific age range used.

Although the average performance was acceptable, there was a large variability between individual recordings. For example, the recall scores for the best performing algorithm ranged from 0.06 to 1 in the training dataset. This means that at worst, automated detection barely found any of the sleep spindles that were visually detected and at best, all of them were found. These extreme values could be a consequence of extremely low numbers of detected sleep spindles both visually or automatically. If only a few sleep spindles were found, which can happen in short naps, the recall values can easily be extreme. However, we did not find a significant correlation between nap duration and recall score, neither using the default settings ($r = 0.05$, $p = 0.81$) or the adjusted settings ($r = 0.05$, $p = 0.78$). Importantly, we show that sleep spindle densities obtained through automated detection with the adjusted algorithm were correlated to a high degree with sleep spindle densities from visual detection, and that this was improved compared to the default settings. This gives us confidence to proceed the analyses in Chapter 5 with the adjusted thresholds.

4.3 K-complexes

K-complexes are researched much less than sleep spindles. A quick search on PubMed (on 3/09/2024) shows 2534 search results for papers analysing sleep spindles and 716 for K-complexes. When constricting the search to infancy, 173 search results remain for sleep spindles, but only 14 for K-complexes. As a consequence, much less is known about the development of K-complexes and specialized automated detection methods for infants are non-existent.

4.3.1 Approaches to detect K-complexes

In adults or children, spontaneous K-complexes are typically measured using visual or automated detection methods (Ameen et al., 2022; Colrain, 2005; Ranjan et al., 2018). According to the American Academy of Sleep Medicine (AASM) a K-complex is: 'A well-delineated, negative, sharp wave immediately followed by a positive component standing out from the background EEG, with total duration ≥0.5 seconds, usually maximal in amplitude when recorded using frontal derivations' (Iber et al., 2007). See figure 4.6 for examples of adult K-complexes. As mentioned in Chapter 1 section 1.1, K-complexes are regarded as a special type of SW, either a forerunner of SWs in N3 (De Gennaro et al., 2000) or as part of a continuum of reactive sleep elements (Halász, 2016). Due to the similarity with SWs, one approach for automated detection is to adapt SW detection algorithms with additional

criteria tailored to a K-complex (Parapatics et al., 2015). Besides automated and visual methods, evoked K-complexes can also be measured by averaging the EEG signal time-locked to a stimulus (Bastien & Campbell, 1992), a technique commonly used in 'wakefulness research', for example in event related potentials. Averaging across trials is helpful to amplify the signal-to-noise ratio. Background noise, if truly random, will average to zero, while any consistent neural response remains visible. Indeed, when averaging across trials during N2, usually an evoked response is visible, albeit much smaller in amplitude than would be expected from individual K-complexes (Weitzman & Kremen, 1965; H. L. Williams et al., 1962). This is because not all trials elicit a K-complex. The likelihood of eliciting a K-complex is dependent on the physical features of the stimulus, such as the intensity and rate of presentation. For example, at 60 Db, a K-complex will be elicited in 25% of the trials, while at 80 Db, 50-60% of trials elicit a K-complex (Bastien & Campbell, 1992). The rate of stimulus presentation matters too, due to the refractory period of K-complex generation, which is between 10-15 seconds (Colrain, 2005). Some studies therefore separate trials into K-complex positive and negative trials before averaging (Ameen et al., 2022; Bastien & Campbell, 1992). The averaged signal then represents the average K-complex more accurately without being influenced by the likelihood of K-complex occurrence. In adults, this approach works well because evoked K-complexes have a distinct shape and reliable timing relative to the stimulus.

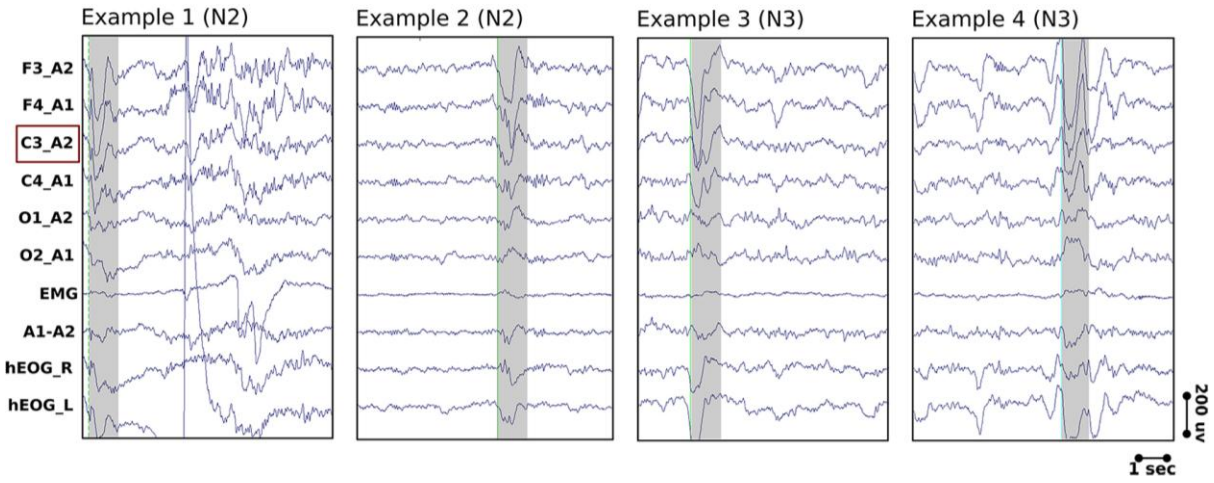

Figure 4.6 Examples of K-complexes in an adult recording. Figure from Ameen et al. (2022).

4.3.2 Development of K-complexes and detection in infancy

As part of the definition, a K-complex is an isolated event that stands out from the background activity (Iber et al., 2007). However, infant sleep EEG is characterised by high voltage background activity (Frey et al., 2016), which makes it challenging to identify a true K-complex that 'stands out'. Metcalf et al. (1971) describe 4 grades of K-complex discernibility across development (see Fig. 4.7 and 4.8). These grades are based on individuation, shape parameters and topographical spread. Before six months-

of-age, K-complexes might be present already, but are almost impossible to distinguish from the background signal (Grade 0). After six months-of-age, K-complexes can be detected, but are still "hidden" within the EEG signal (Grade 1). Around two years of age, K-complexes become more easily discernible, although EEG background activity is still high in childhood (Grade 2). Metcalf and colleagues conclude that until 7 years of age, when K-complexes reach Grade 3, differentiating K-complexes is challenging. In line with Metcalf et al., but in a larger sample of 50 infants, using repeated measurements at 2 weeks, 3 months, 6 months, 9 months and 12 months, Verma & Baisakhiya (2021) show that spontaneous K-complexes are not visible before 3 months of age. Between 3 and 6 months, K-complexes start to emerge. However, when K-complexes become visible depends on the individual. At 9 months, 10% of infants (4/40) still did not have any visible K-complexes. By 12 months, this number decreased to 5% (2/38). Thus, while spontaneous K-complexes generally start to emerge before 6 months, there is considerable variability among infants. In addition, the shape of the K-complexes changes from blunt at 6 and 9 months to mostly sharp at 12 months. Again, some infants still have blunt K-complexes at 12 months (8%), showing that individual maturational trajectories are highly variable.

While the studies mentioned above looked at spontaneous K-complex development, one study in 5 month-old infants investigated evoked K-complexes, focusing on the effects of smoking during pregnancy (King et al., 2018). In this study, K-complexes were detected visually in a 1400 ms window after stimulus onset, but it is unclear which criteria were used for visual detection. In the control group (infants not exposed to nicotine), K-complexes were elicited in response to 85 dB paired clicks in 28% of the trials on average, with a range of 9.5 to 41%. This suggests that by 5 months infants are capable of producing K-complexes in response to stimulation. It is unclear whether those infants that did not show any spontaneous K-complexes in Verma & Baisakhiya's study would however be able to produce *evoked* K-complexes.

Figure 4.7 Grade of K-complex maturity across development. Figure from Metcalf (1971)

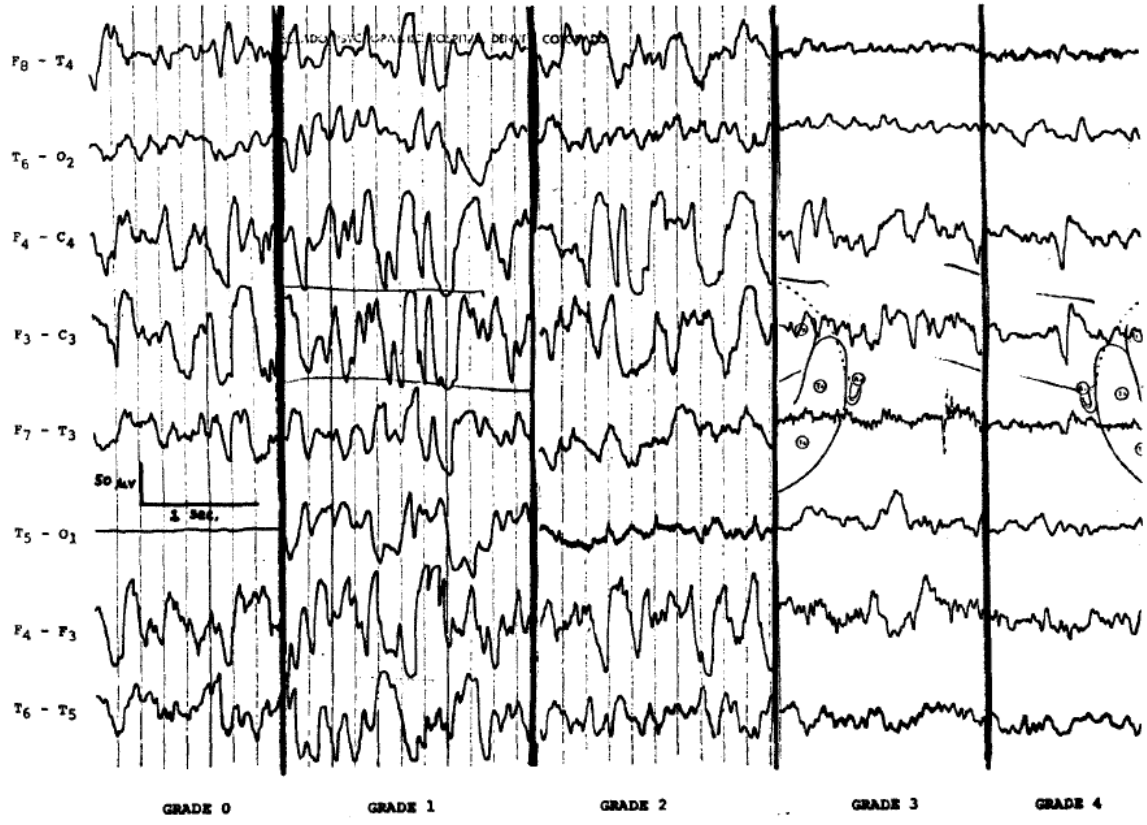

Figure 4.8 Example data of different levels of K-complex maturity. Figure from Metcalf et al. (1971).

4.3.3 K-complexes detection in the SNOOSE study

4.3.3.1 Rationale and justification

In 8-11 month-olds (the age range of the SNOOSE study), K-complexes are still difficult to distinguish from the background signal. According to Metcalf's discernibility scale, K-complexes fall into Grade 1 around that age. Moreover, at this age, the characteristic sharpness of K-complexes is underdeveloped, often appearing more blunt (Verma & Baisakhiya, 2021), which further complicates detection. Without clear guidelines on what should be considered a K-complex at this age range, visual detection likely results in unreliable estimates that vary between scorers. Reliable visual detection is a crucial step in the improvement or development of automated detection algorithms. Furthermore, open source and easy-to-use algorithms are not as abundant for K-complex detection compared to sleep spindle detection. Therefore, we decided it was not feasible to adopt the same approach as we did above for sleep spindle detection.

Instead, we decided to tap into the precise timings of *evoked* K-complexes. We aimed to explore whether evoked K-complexes could be detected automatically using YASA's slow wave detection algorithms. In adults, there is a well-defined and reliable time-window in which K-complexes appear in response to sensory input. Specifically, the negative peak of an evoked K-complex occurs between 450 and 700 ms after stimulus onset (Forget et al., 2011). However, it is unclear whether these timings are the same in infants age 8-11 months old. Averaged evoked K-complex responses in 5-month-olds indicate a peak around 450-500 ms after stimulus presentation. We therefore wanted to check if we could see an increase in detected SWs in the 450-700 ms time window in this age range using an automated SW detector.

This approach allows us to circumvent two key challenges regarding K-complex detection in infants. Firstly, while the human eye might have difficulty separating a K-complex from the background noise, an automated approach might have less problems doing so. Secondly by focusing on evoked K-complexes which have a predictable timing relative to the stimulus, we can bypass some of the ambiguity that makes spontaneous K-complex detection difficult in this age group.

4.3.3.2. Methods and results

All pre-processing steps were identical to those used in the sleep spindle detection (see 4.2.3.2.2.). K-complexes were detected in N2 only using YASA's slow wave detection algorithm. Most of the default setting were used, including a frequency band of 0.5 – 2 Hz, a negative peak duration of 0.3-1.5 seconds, and a positive peak duration was 0.1-1 second. However, due to high slow waves amplitudes in infancy compared to adulthood (Frey et al., 2016), the upper limits of the negative (>50µV) and positive (>20 µV) peaks and peak-to-peak amplitude (>75 µV) were removed.

In the SNOOSE study, a total of 34 naps were recorded whilst auditory stimulation was played, where 60 dB pure tones were presented in pairs (S1 and S2) every 12-18 seconds (see Chapter 5 for more details on the stimulation). Of those 34 recordings, two were excluded: One recording did not have any trigger markers due to technical failure and one recording had a noisy Cz channel. This leaves a total 32 sleep recordings that were included in these analyses. In adults, K-complexes amplitudes are largest in frontal regions (Iber et al., 2007) in children however amplitude maxima are seen over central areas (Melendres et al., 2008). Therefore, K-complexes were detected in channel Cz. Detection was performed on 16 second long artefact-free N2 segments that started at -4.15 and ended at 12.35 seconds time-locked to S1. This length was chosen to meet the minimum length requirement for the algorithm to detect SWs.

Figure 4.9 shows an example of SWs detected by the YASA algorithm in a segment during stimulation (S1 onset is 0.0 in the figure). YASA filters the raw data in the 0.5 – 2 Hz frequency band (Fig. 9B). In adults, the negative peak of K-complexes is expected between 450-700 ms (see blue shading in Fig. 4.10). In this example, none of the detected SWs have a negative peak within the 450-700 ms post-stimulus window and they would therefore not be classified as evoked K-complexes.

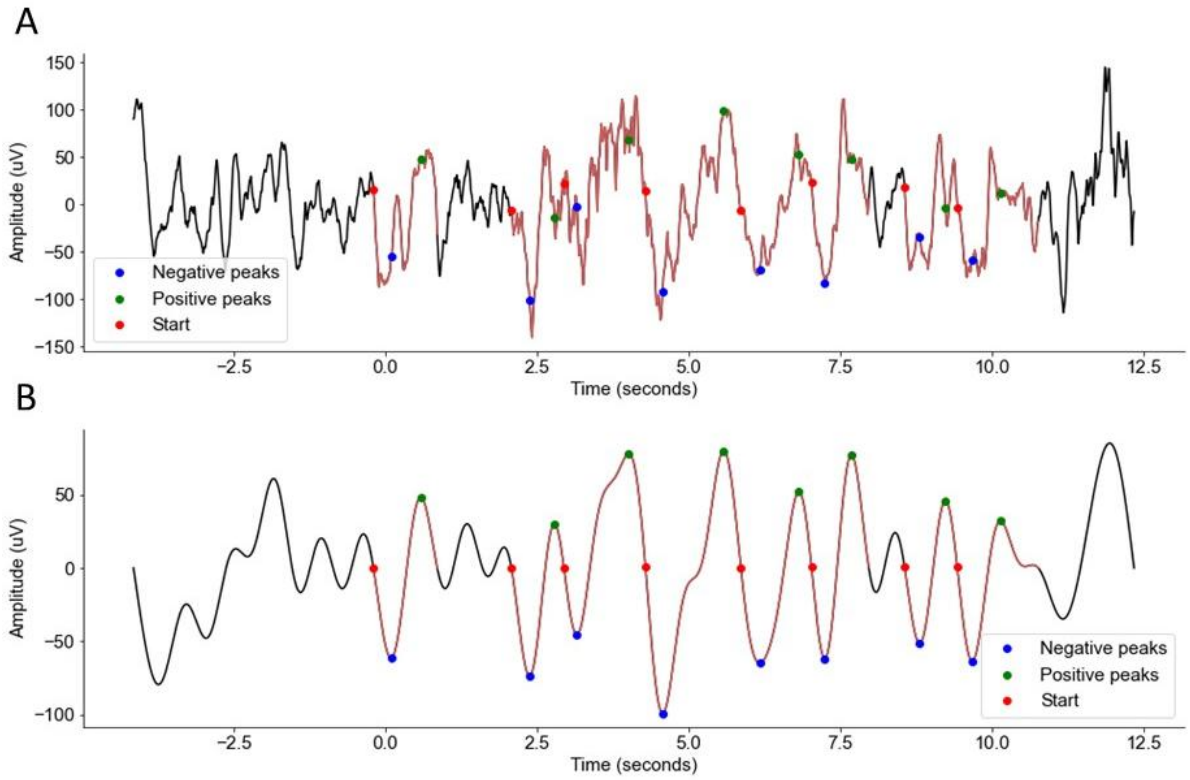

Figure 4.9 Example of SWs detected by YASA in channel Cz. Time 0 is the onset of an auditory stimulus. A. Detected SWs in the raw data. B. The same detected SWs in the filtered data with a 0.5-2 Hz bandpass filter.

Across all recordings, a total of 3571 SWs were detected in artefact-free N2 segments. A clear increase in the production of SWs was observed following S1 and a slight increase following S2 (see figure 4.10). In the 450-700 ms window after S1, 145 SWs were detected, and 126 SWs after S2. For comparison, only 90 SWs were detected within a time window of the same length before the stimuli. Therefore, we concluded that this time-window is appropriate to use in this age range as well.

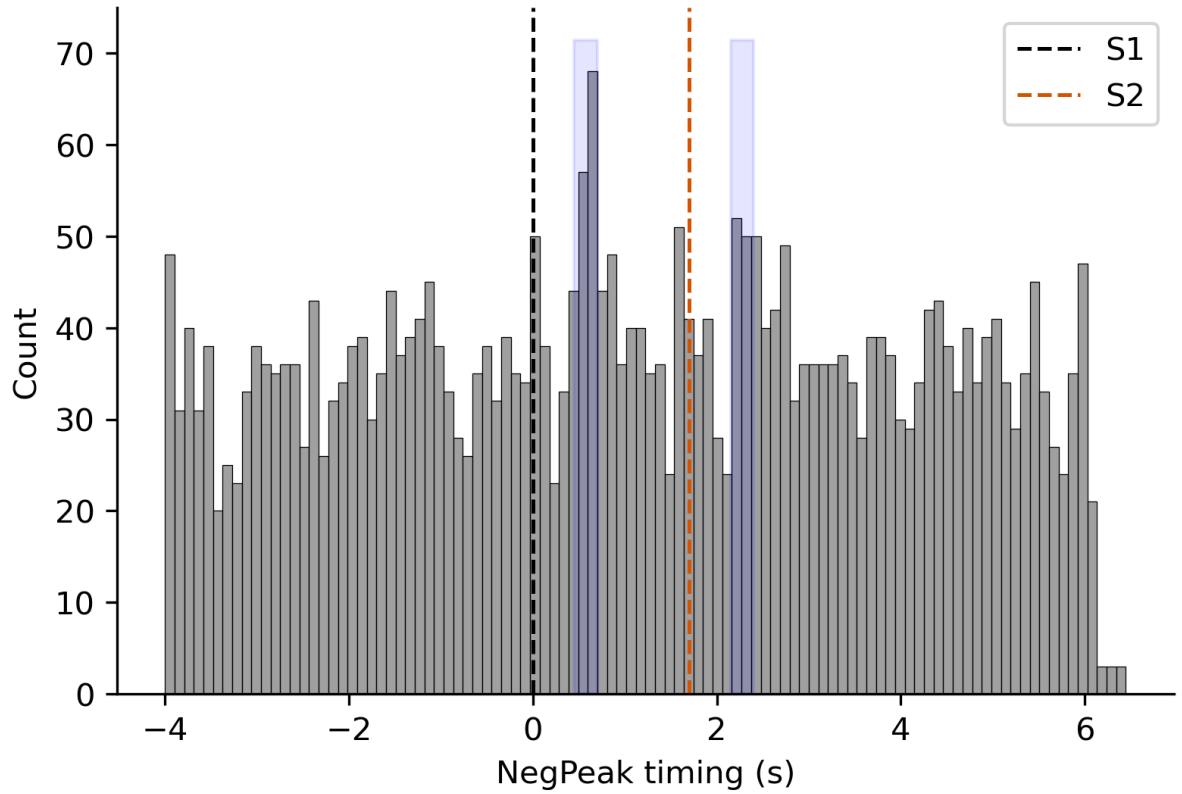

Figure 4.10 Timing of the negative peaks of automatically detected slow waves in the time window around auditory stimuli S1 and S2. A clear increase in SWs can be seen after S1. The blue shading shows the expected time windows for the negative peaks based on adult literature (450-700 ms post stimulus onset).

There are several limitations using this approach. For example, many of the SWs detected in the post-stimulus window may actually not be evoked K-complexes, but rather ongoing SWs, which seems likely given the high number of detected SWs throughout the entire segment. Moreover, these detected SWs may still be *spontaneous* K-complexes or SWs. To rule out this possibility, in the following chapter, analysis will always involve a comparison with detected SWs in a window before stimulus onset.

A potential future improvement to this method could be to select detected SWs that are not followed by another SW immediately, because, as part of their definition, K-complexes are isolated events. This could potentially exclude some ongoing SWs and improve the precision of K-complex detection.

4.4 Summary and conclusion

There are unique challenges to reliably detect sleep spindles and K-complexes in infants age 8-11 months old. For both events, literature that characterises developmental trajectories in the first year of life is limited. For K-complexes in particular, the literature is almost non-existent. Without clear age-dependent guidelines for visual identification for K-complexes, it is impossible to establish a reliable 'ground truth', necessary for the development of automated methods.

For sleep spindles, features such as sleep spindle duration, frequency and amplitude are still maturing and likely at a different pace for each individual. In open-source algorithms, such as YASA, frequency ranges and duration are often easily adapted. However, low amplitudes of sleep spindles and high background activity can result in underdetection of sleep spindles compared to visual detection when algorithms are trained on adult data. Indeed, using YASA's default thresholds, sleep spindles were underdetected in the SNOOSE sample. Adjusting the thresholds based on optimal performance in a training dataset successfully improved algorithm performance in a validation dataset. However, it should be mentioned that the improved algorithm could be further improved, as it shows 'acceptable' performance scores. However, these scores are similar to other algorithms used in the field. High correlations between sleep density obtained by the improved automated detection and visual detection gave us confidence to continue with this algorithm for the analyses in Chapter 5.

For K-complexes, we focus on evoked K-complexes due to the predictable timing in response to a stimulus. Additionally, an automated detection method is chosen over visual detection due to the difficulty discerning K-complexes from background activity. In the SNOOSE sample, we see a clear increase in automatically detected SWs in the expected time-window. Going forward, we will use this method to detect evoked K-complexes.

Chapter 5.
Auditory input during an infant nap and the interaction with sensory profiles

5.1 Introduction

Chapter 1 showed that sensory processing is dependent on vigilance state. The dual needs during sleep - the protection of the sleeping brain from interference and responsiveness to salient stimuli - are managed by sensory gating and gaining. Throughout this thesis, a potential causal relationship between sleep and sensory atypicalities is explored. In this chapter, I focus on whether infants that are more responsive to sensory input during wakefulness show atypical markers of sensory (dis)connection during sleep. Understanding how sensory input interacts with these sleep features could help to unravel why these infants have sleep difficulties.

Two key aspects of sensory processing during sleep can be disentangled: The *influences* of sleep *on* sensory processing and the *consequences that* sensory processing have on sleep. The former is concerned with the spontaneous ongoing activity that determines to what extent an incoming stimulus is processed, while the latter relates to the reactive or evoked response to sensory input. One potential mechanism that links sleep and sensory processing atypicalities is that spontaneous sleep rhythms related to sensory (de-)coupling are altered in individuals that have sensory atypicalities, which would make their sleep more susceptible to external sensory disruption. Another possibility is that, in the absence of environmental sensory disturbance, there are no differences in sleep between individuals with sensory differences, but once external sensory input is introduced or increased, the evoked brain responses are altered in individuals with heightened sensory atypicalities.

According to the framework proposed by He et al. (2023), there are multiple aspects of sensory processing differences in autism, which cannot be thought of as homogenous. Throughout this thesis two aspects of sensory processing have been captured: an objective, neural measure of sensory processing (which I referred to as sensory gating), and a subjective behavioural measure (low threshold). The latter taps into affective and behavioural reactivity to sensory input and is assessed through the Sensory Profile, a caregiver report (ITSP or SP-2, (Dunn, 2002, 2014)). In this chapter, we again use the ITSP low threshold measure, for a couple of reasons. Firstly, this measure, and in particular this questionnaire, has been by far the most commonly used measure of sensory differences in relation to sleep in autism (Lane et al., 2022). Therefore, to understand the underlying mechanism of the frequently reported association between sleep and sensory processing, it seems intuitive to use a similar measure. Secondly, in this study, we want to capture sensory processing during wakefulness as a stable trait, rather than a time-specific fluctuation. The questionnaire asks about the frequency of an individual's behaviours and therefore captures an infant's sensory profile as a trait. Indeed, the results from chapter 3 also indicate that low threshold is highly stable over time within the same individual. Thirdly, the results from chapter 2 show that low threshold maps onto sleep more broadly,

both sleep onset and night awakenings, while the neural measure of sensory gating seems to associate with specific features of sleep only (i.e. sleep onset).

The aim of this chapter is to understand whether brain activity, related to sensory (de-)coupling during sleep, differs during undisturbed sleep (baseline condition) or when auditory stimulation is presented during sleep (stimulation condition) in individuals with a variety of sensory processing profiles. Using a within-subject design, where infants at typical and elevated likelihood for autism take a nap in a baseline and a stimulation condition, allows us to capture both spontaneous and evoked activity during sleep in relation to variation in sensory profiles.

In the section below, features of sleep that are expected to influence and be influenced by sensory input are discussed. These will be divided into features that have been linked to sensory disconnection during sleep, which are therefore protecting sleep, and features that are markers of sensory disconnection, disrupting sleep. Slow waves (SWs) and sleep spindles are discussed as sleep protective elements, and markers of arousal will be discussed as sleep disruptive elements.

5.1.1 Sleep protection

5.1.1.2 Bistability: Slow waves and K-complexes

As described in detail in Chapter 1 section 1.1.1, one mechanism that could gate sensory input during NREM sleep is the bi-stable dynamics of neuronal populations, reflected as large SWs in the cortex. In short, SWs may limit sensory processing by disrupting cortico-cortical communication and therefore establishing a *cortical gate* during NREM sleep. That SWs de-couple the sleeper from their sensory environment is supported by the fact high SWA is related to high arousal thresholds and the higher SWA before a stimulus (Neckelmann & Ursin, 1993), the less likely a behavioural arousal will follow (Hayat et al., 2020). These SWs can be considered spontaneous, because they are not evoked by sensory input. However, SWs can also be evoked. One special type of SW, the K-complex, is particularly known for its reactive nature. K-complexes can most easily be seen and measured in sleep stage N2, when they stand out from the background activity. Whilst K-complexes appear in response to stimulation they also occur spontaneously without any known sensory input. In this Chapter, I focus on SWA as a feature of SWs, because it is most commonly used and as mentioned above is known to capture 'sleep protection'. Due to the challenges of measuring K-complexes in infants (See Chapter 4), K-complexes are measured in N2 as evoked SWs in response to the auditory stimulation during the stimulation condition.

Relationship with sensory profiles and autism

Here, we are interested in how variability in sensory profiles determines spontaneous and evoked markers of sensory disconnection. To our knowledge very few studies have looked at the relationship

between SWs and sensory processing differences. One study, that was mentioned before, shows that K-complexes are less likely to be elicited by high volume noise in adult participants that rate themselves highly on a noise sensitivity questionnaire (Lechat et al., 2021). This shows that a person's sensory profile may indeed determine responses to sensory input during sleep.

Whether slow waves are atypical in autistic individuals is still unclear with mixed findings in the literature. In 4 year-olds with autism, SWA is lower and the slope of the SW is shallower in the first part of the night compared to controls (Arazi et al., 2020). Other studies in both older children and younger toddlers do not find any differences in SWA between autistic and typically developing children (J. Nguyen et al., 2022; Page, 2018). Nguyen et al (2022) did not distinguish between different parts of the night, which could explain why they did not find any differences in SWA between groups. None of these studies looked at a specific association with sensory processing differences. These studies focussed on spontaneous SWs, but it is unclear whether evoked responses, such as K-complexes, are altered in autistic individuals.

5.1.1.2 Sleep spindles

Another feature of sleep which has been proposed to contribute to (or be a correlate of) sensory disconnection are sleep spindles. The spindle gating hypothesis proposes that sleep spindles serve as protective elements, shielding the cortex from external input and thus promoting sleep maintenance. In Chapter 1 section 1.1.1, I describe that some studies indeed show that sensory input is gated during a sleep spindle event (Schabus et al., 2012) and that the arousal threshold is higher during a spindle (Wimmer et al., 2012) or in periods when sleep spindles are abundant (Cardis et al., 2021; Lecci et al., 2017). However, not all findings align with this view (Rudzik et al., 2018; Sela et al., 2016). Moreover, whether sleep spindles passively protect the brain from sensory interference or whether they are reactive elements and are upregulated in the face of noise is also still debated, with evidence for (Ameen et al., 2022; Sato et al., 2007) and against an upregulation of sleep spindles (Rudzik et al., 2018).

Relationship with sensory profiles and autism

A decrease in spindle density has been observed in children and adolescents with autism (Chilakamarri et al., 2017; Farmer et al., 2018; Mylonas et al., 2022). Activity in spindle frequency range (10-16 Hz) is decreased in infants with autism compared to controls as young as 12-30 months; lower spindle activity is associated with higher autism symptom severity (Page, 2018). It still remains unclear whether reduced spindle activity is related to particular symptoms of autism. One possibility is that sensory processing atypicalities and sleep spindle generation reflect common underlying mechanisms. For example, both sensory sensitivities and disrupted sleep spindle generation could be caused by

atypical functioning of the thalamus. Thus, previously described associations between sensory sensitivity and poor sleep in infants with older autistic siblings may be mediated by alterations in sleep spindle generation. To our knowledge, this has not been looked at in autistic individuals. However, in typically developing 4-year-olds measures of sensory gating and sleep spindle features are related to each other (P.-P. Wei et al., 2017), suggesting that variability in sensory processing could potentially be linked to sleep spindle atypicalities.

In summary, we ask whether infants with sensory differences show disruptions in neural measures previously related to sensory disconnection. Studies in autistic individuals suggest a decrease in spontaneous SWA and sleep spindle density, but they did not investigate whether the decrease was particularly related to sensory atypicalities. Subjective sensitivity scores in non-autistic adults are associated with diminished evoked responses, suggesting that perhaps both spontaneous and evoked responses to sensory input could be affected. We hypothesize that individuals with a low threshold, that are more reactive to sensory input, will show decreased sleep protective elements, either spontaneous or evoked or both.

5.1.2 Sleep disruption

Arousibility is the capability to be awakened from sleep by sensory input. It also encompasses intermediate levels of wakefulness that blend with sleep. During sleep, transient phases of activation occur spontaneously or induced by an external event, without necessarily leading to wakefulness (Schieber et al., 1971). These transient arousals during sleep are part of healthy sleep (Halasz et al., 1979). Failing to wake up when faced with harmful stimuli can have detrimental consequences, such as sudden infant death syndrome (Kahn et al., 2003). Arousal frequency also follows a developmental trajectory, decreasing throughout the first year of life (Grigg-Damberger Madeleine et al., 2007; Montemitro et al., 2008). Although arousals during sleep are natural and necessary, excessive sleep fragmentation can negatively affect next-day functioning, leading to increased daytime sleepiness and lower mood (Bonett, 1985; Martin et al., 1997; Stepanski, 2002). Moreover, it can increase long-term health risks (E. J. Van Someren et al., 2015). Therefore, a balance is essential to maintain the reversibility of sleep when needed, but not fragment sleep too often.

An arousal is characterized by autonomic responses, such as increased heart rate or blood pressure, muscle activation and cortical activation, which occur in a hierarchical order. However, a stimulus does not necessarily activate the whole pathway, but can also partly activate it, e.g. only autonomic responses and increased muscle tone, but not visible cortical activation (Davies et al., 1993). The same continuum of arousals in response to a stimulus has been documented in young infants (McNamara et al., 1998). Arousals are under influence of circadian and homeostatic forces, occurring more during

the 2nd part of the night and less during rebound sleep (Halász et al., 2004). Humans and mice show infra-slow fluctuations during sleep, with phases more and less vulnerable to external perturbation during sleep (Lecci et al., 2017; Yüzgeç et al., 2018).

In this study, we measure infant naps and therefore do not focus on awakenings, which are more likely to occur in longer sleep periods, such as a night sleep. Instead we focus on arousals, with and without cortical activation, as it is known that they can trigger sleep stage transitions, fragment sleep and impact next day functioning (Martin et al., 1997; Stepanski, 2002). There are multiple ways of measuring arousibility. One way is to measure the frequency of arousals, by detecting arousals as discrete events based on a set of definitions. Another way is to measure cortical arousibility through the activation index (AI), defined as the ratio of activity in the beta- over delta band. A synchronized reduction in delta power and increase in beta power can be induced by the stimulation of the reticular formation, which plays a major role in promoting wakefulness (Moruzzi & Magoun, 1949). In mice, peaks in AI tend to co-occur with micro-arousals or increases in heart rate (Cardis et al., 2021). The AI is also higher in mice with chronic neuropathic pain, which suggests a link between this index and sensory processing. Interestingly, in humans a higher AI can predict subjective underestimation of sleep (individuals perceive their sleep worse than it was according to objective measures), whilst the number of arousals does not (Fasiello et al., 2024; Lecci et al., 2020). This suggest that both measures, although related, perhaps tap into different mechanisms. Lecci et al (2020) suggest that AI captures long-lasting increased activity of 'subthreshold' arousals systems compared to suprathreshold transient arousals. The AI is therefore a better measure of arousibility throughout sleep.

Here, we explore whether infants with sensory atypicalities show increased sleep neurophysiological measures of sensory connection, both spontaneous and evoked. We hypothesize that individuals with a low threshold, that are more reactive to sensory input, will show increased markers of arousibility, either spontaneous arousals or arousals evoked by sensory input or both.

5.1.3 Analysis approach

Sleep protective and disruptive elements during sleep will be analysed on two scales. First, we will investigate micro-scale responses to stimulation. This approach allows us to understand immediate changes in brain activity following a stimulus. Specifically, we will compare neural activity before and after the stimulus to elucidate underlying mechanisms.

Second, we will explore macro-scale processes across the duration of a nap. Studies have demonstrated that sensory input can influence sleep patterns on a larger scale. For instance, research using models of sensory deprivation has shown significant alterations in sleep stages. For example, guinea pigs with cochlear removal exhibit increased slow wave and REM sleep, and decreased

wakefulness (Pedemonte et al., 1997). Similarly, deaf humans experience changes in sleep stages upon activating their cochlear implants, transitioning from reduced N2 and REM sleep to increased N3 sleep (Velluti et al., 2010). This suggests that sensory input accumulated over the course of a nap may affect sleep differently and potentially impact daily functioning to a greater extent. The analyses of this chapter will be divided into micro-scale responses, focusing on immediate neural reactions to stimuli, and macro-scale processes, exploring the broader effects of sensory input on sleep stages over the course of a nap.

5.2 Methods

5.2.1 Experimental model and subject details

Forty-four infants, age 8 – 11 months, participated in a nap study, consisting of two visits (Baseline and Stimulation condition). Four infants did not fall asleep, but one of those infants returned another day and managed to fall asleep at their second go. A total of 41 infants napped at least once in the lab (female = 23). Thirty infants completed both visits, however data of infants that only completed one visit was also included in analysis (See figure 5.1), resulting in a total of 71 sleep recordings. The study recruited infants with an older sibling with or without an autism diagnosis. Infants were classified as being at elevated likelihood for autism (EL) if they had an older sibling diagnosed with autism or undergoing diagnosis (n = 8, female = 3). Infants without an autistic first-degree relative were considered at typical likelihood for autism (TL; n = 35). Participants were recruited on a voluntary basis through the university participant database and adds on social media. Organisations and charities related to autism were contacted as well to advertise the study. Participants received a £10 voucher for each visit and they received reimbursement for travel and accommodation if needed. They also received a book at the first visit and a T-shirt at the second visit.

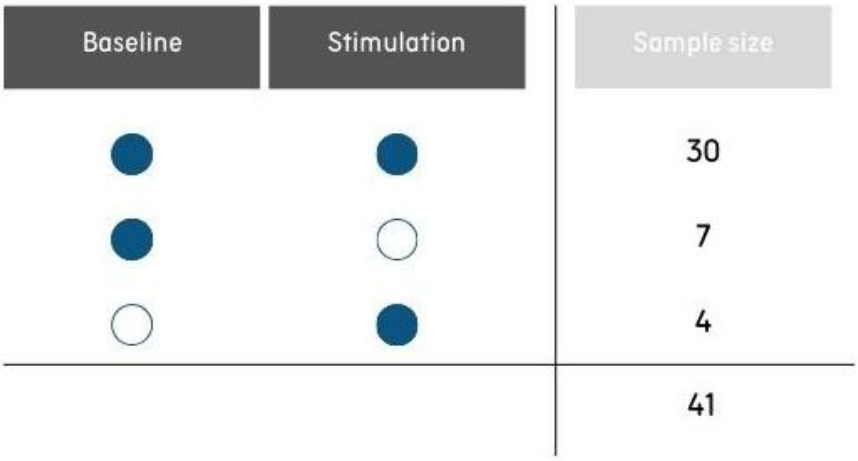

Figure 5.1 Study completion. Baseline and stimulation condition were counterbalanced. Sample size refers to the number of participants, not number of recordings.

5.2.2 Study procedure

Infants and their caregivers were invited for two visits at the sleep laboratory at the University of East Anglia, UK. Ethical approval was given by the Ethics Committee of the School of Psychology of the University of East Anglia (ethics reference code: ETH2324-0296). Participants arrived just before infant's usual naptime and were asked to come back at the same time for their second visit. The majority of infants took part in a morning visit, between 8 am and 1 pm. Five infants visited the lab in the afternoon, between 1 and 5 pm. The time between visits was 15 days on average (SD = 14), but ranged from 2 to 61 days. Caregivers were encouraged to settle their infant as they normally would. Infants slept either in the caregiver's arms on an armchair (n = 29), in a cot or on a bed alone (n =12). Again, we ensured this was consistent across the two visits. When possible, caregivers filled out questionnaires during the nap, otherwise they filled them out at home. An experimenter stayed in the room with the caregiver and infant, making notes during the session. Caregivers were encouraged to let their child nap until they woke up naturally. However, on four occasions caregivers woke the infant up prematurely for practical reasons (e.g. pick up the older sibling from nursery).

Infants napped in two different conditions: *baseline* and *stimulation*. The order of conditions was randomly counterbalanced across the study (Fig. 5.1.). In the stimulation condition, auditory stimulation was played from two speakers which were positioned approximately 50 cm from each ear. The stimulation was started once the infant was asleep for a couple of minutes. Auditory input was applied in the form of 60 dB 225 Hz pure tones, lasting 1 sec each and presented in pairs, S1 and S2 (Fig. 5.2). The volume was set at 60 dB to make sure this was below the arousal threshold whilst still being noticeable. Previous studies in infants show that the arousal threshold for auditory stimuli tends

to be between 70 and >100 dB (Franco et al., 1998; Trinder et al., 1990). The intra-stimulus interval was 700 ms and the interval between pairs varied randomly between 12-18 seconds. This interstimulus interval and jitter were chosen to minimize habituation to and anticipation of the stimulus. The total number of pairs of stimuli depended on the nap length, was 175 on average and ranged between 89 and 325.

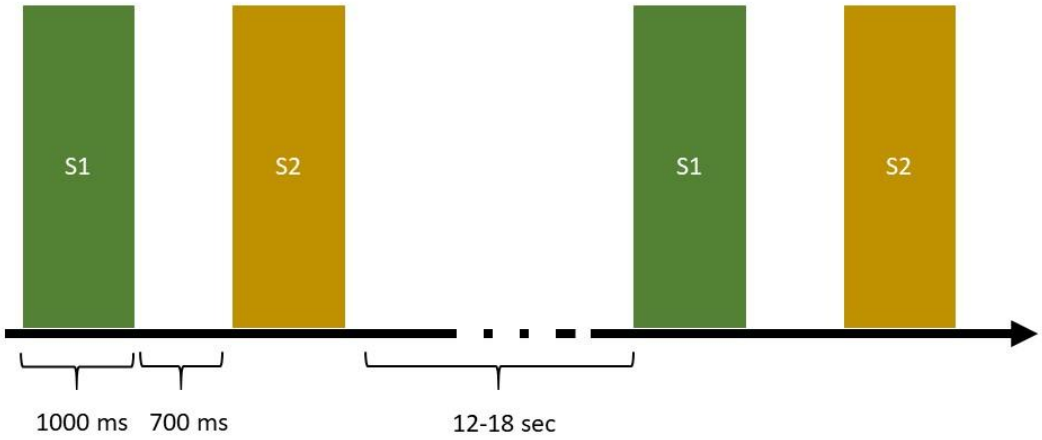

Figure 5.2 Stimuli design. Pairs of stimuli (S1 and S2) were presented in a jittered interval every 12-18 seconds. Each stimulus lasted a 1000 ms and the time between stimuli was 700 ms.

5.2.3 EEG data acquisition

Brain activity was recorded using a wearable LiveAmp with 32-channels (Brain Products GmbH, Gilching, Germany) placed within an EEG sensor cap according to the 10-20 system. Different cap sizes were available, sized to the infant's head circumference (ActiCap snap, Brain Products GmbH, Gilching, Germany). Four out of thirty-two electrodes (FT9, P7, P8 and FT10) were used to measure electrooculography (EOG) and electromyography (EMG). The sampling rate during data acquisition was 500 Hz and the online reference was FCz.

5.2.4 Pre-processing and sleep staging

All pre-processing steps were performed in MNE python (Gramfort et al., 2013). Data was filtered between 0.2 and 40 Hz using a 1st order butterworth bandpass filter. Notch filters at 50, 100, 150 and 200 Hz were added to exclude line noise. Data was re-referenced offline to the contralateral mastoids for sleep staging and visual arousal detection. Manual sleep staging was performed using the graphical user interface Sleep from Visbrain, a python based package (Combrisson et al., 2017, 2019). Sleep staging was done on 30 s epochs by two individual scorers based on the AASM criteria and guidelines from the Pediatric Task Force (Grigg-Damberger Madeleine et al., 2007; Iber et al., 2007). All hypnograms were compared between the two scorers. Where the hypnograms deviated from each other, the scorers discussed until an agreement was reached. Visually detected arousals, minimal 3 sec, were marked on the hypnograms. Arousals detection was based on guidelines from the

International Pediatric Work Group (The International Paediatric Work Group On Arousals, 2005) and The Pediatric Task Force (Grigg-Damberger Madeleine et al., 2007). See section 5.4.1.1.4 for more information on the definition of an arousal. Automatic artefact rejection was performed in all sleep stages using the artefact rejection function from YASA using a 1 sec window (Vallat & Walker, 2021).

5.2.5 Low Threshold from the SP-2 Questionnaire

In Chapter 3, sensory processing was measured with the Infant/Toddler Sensory Profile (ITSP) using a combination of the sensory sensitivity and sensation avoidance subscales, referred to as the 'low threshold'. Since data from the BASIS study was collected, Dunn has published a second version of the ITSP, the Sensory Profile 2 (SP-2, (Dunn, 2014)), which we decided to use in the SNOOSE study. The SP-2 adopts a similar theoretical framework as the ITSP but does not use the term low threshold (LT) anymore to describe the combination of sensory sensitivity and sensation avoidance. However, to be consistent with the previous chapters, we decided to continue using this construct. Although many questions remain the same in the SP-2 compared to the ITSP, some questions were dropped, added or moved quadrant. According to Dunn, this is due to the data-driven approach and because perception and interpretations of behaviours changed over the 20 years that passed between the construction of the ITSP and SP-2 (personal correspondence with Dunn on 11-08-2022). In the SP-2, the avoidance quadrant consists of 11 questions and the sensitivity quadrant consists of 12 questions. Both quadrants contain questions from general, auditory, oral, touch and behavioural modality. Sensitivity additionally consists of one question from the movement modality (see a list of all questions in Appendix B table A.4). Overall, both versions are still largely similar, likely capturing the same concepts. The age-appropriate version, 7-36 months, of the SP-2 was used. Another change in the SP-2 is that caregivers have the option to answer 'not applicable'. LT was calculated by taking the average score of all questions that were not marked as 'not applicable' on the sensory sensitivity and sensation avoidance scales per individual. Forty-nine percent of caregivers completed all questions of the LT subscale. However, 20% of participants answered 'not applicable' to more than 25% of the questions. The high frequencies of 'not applicable' likely reflect a high variability in developmental milestones in 8-11-month-olds and the inappropriateness of some questions for infants at the lower end of the intended age range (7-36 month-olds). For example, one of the questions which was answered 'non-applicable' by 23% of responders was '*My child prefers one texture of food (for example, smooth, crunchy)*'. It is possible that not all infants have started solid foods by 10 months of age, when invited to our study. No participants were removed based on the amount of missing/not applicable answers. See figure 5.3 for the distributions of LT scores in infants at EL and TL in the SNOOSE sample compared to the BASIS sample used in Chapter 3. The range of LT scores is narrower in the SNOOSE study, with less high scores compared to the BASIS study. I discuss potential reasons for this in Chapter 6 section 6.3.

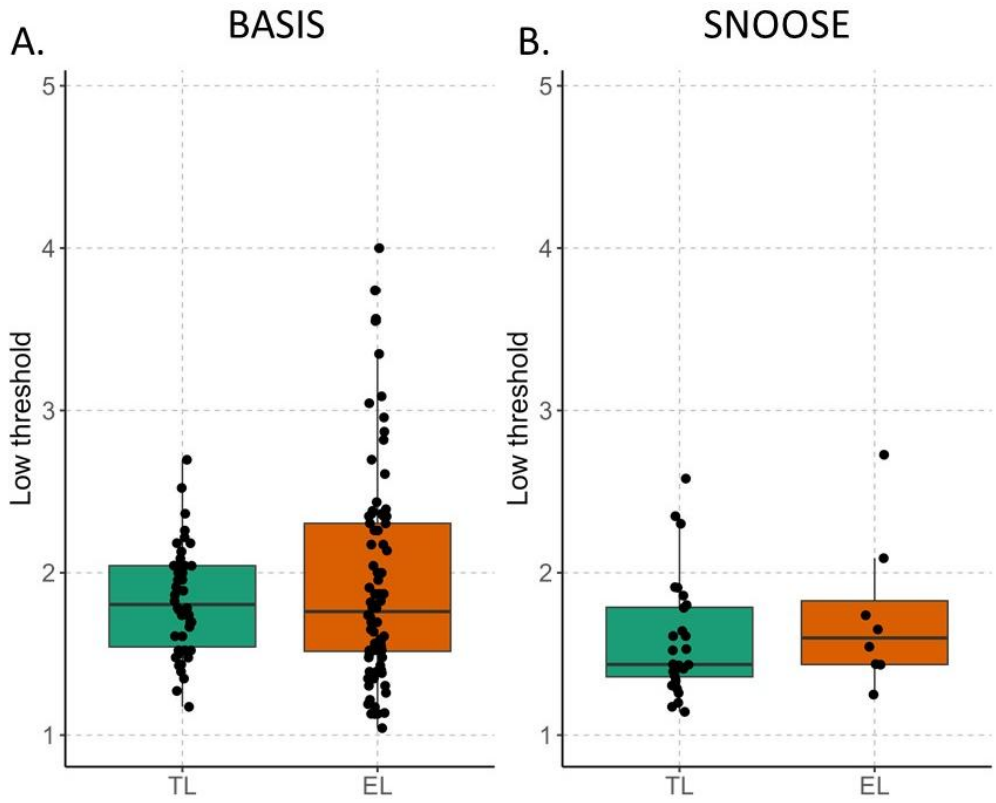

Figure 5.3 Boxplots of Low Threshold in the BASIS (A) and SNOOSE (B) study split by autism likelihood status. In the BASIS study the first version of the Infant/Toddler Sensory Profile questionnaire was used. In the SNOOSE study the second version, the SP-2, was used.

The analysis in this chapter will be divided in two parts. The first set of analyses are exploratory and focus on time-locked responses to the stimuli in the stimulation naps only. Here we aim to understand whether auditory input is registered by the sleeping infant and what the immediate effects of the stimulation are on the ongoing brain activity. The second set are pre-registered analyses which focus on the comparison of the two nap conditions: with and without auditory stimulation. The first analyses explore the immediate responses to the stimulation, while the second ones compare features across the whole naps.

5.3 Time-locked responses to stimulation

The main aims of this study are to examine whether sleep is affected by an individual's sensory profile, by sensory stimulation and/or by the interaction of both. In this part, we focus only on recordings made during the Stimulation Condition but compare EEG measures taken after (ON windows) and before stimulation onset (OFF window). These measures are time-locked to stimulation and evoked by it. The main aims of this section are:

1. To visualise the responses evoked by the stimulation during sleep, by computing ERPs and TRFs to S1-S2.

2. To test whether sleep spindles and K-complexes are evoked by auditory stimulation, by comparing the likelihood of the events occurring before and after S1-S2 and to test whether these evoked responses are different depending on an infant's LT score.

5.3.1 Methods

A total of 34 stimulation naps were recorded, one recording was excluded that did not have any trigger markers due to technical failure. Other exclusions based on bad channels are mentioned separately for each analysis.

There are multiple ways to approach time series data in a time-locked manner. One way is to look at event-related potentials (ERPs). ERPs average EEG activity across multiple trials per subject time-locked to the start of a stimulus. ERPs are a powerful tool to provide precise temporal resolution of responses to stimulation compared to baseline activity, but give a combined output for all frequency bands. Time-frequency representations (TFRs), extract not just time resolved signal, but time-resolved *frequency* representations of the data. Adding this extra dimension in the frequency domain, provides additional information about neural oscillations and neurophysiological mechanisms associated with those oscillations. As a first step, event-related potentials (ERPs) are plotted to visually assess whether the stimulation is registered during sleep. Subsequently, TFRs allow us to make inferences about the neurophysiological mechanisms triggered by the stimulation. Finally, we explore whether a stimulus elicits a demarcated event, such as a k-complex or a sleep spindle. In summary, the effect of stimulation will be explored by investigating changes over time in the EEG signal overall (ERPs), oscillations (TFRs) and elicited events. All time series analyses were performed in MNE python (Gramfort et al., 2013).

5.3.1.1 Event related potentials

ERPs are plotted in the central channels, as the mean of C3, Cz and C4, in artefact-free NREM (N2 +N3) epochs. Out of 33 stimulation recordings, 4 recordings were excluded because of one or more bad channels in the central region, leaving a total of 29 recordings. The analysed epochs were timelocked to S1, started 1.0 second before S1 and ended 3.4 seconds after S1 onset. This ensured that both S1 and S2 were included in the same epoch. Baseline correction was applied to each individual epoch by calculating the mean signal in the second before S1 onset and subtracting it from the entire epoch. On average, 115 epochs were included per individual, with a minimum of 59 and maximum of 201.

5.3.1.2 Time frequency representations: Morlet Wavelets

The Fourier transform is often used to obtain frequency representations of EEG data, but it cannot track frequency changes over *time.* Here we are interested in tracking changes in the power of oscillations in response to the stimuli, and thus across frequencies and time. One common method to calculate TFRs is through Morlet wavelets. Morlet wavelets are sine waves with a Gaussian taper (See

Fig. 5.4). A Morlet wavelet can be thought of a small window that moves along the EEG signal and calculates how well the wavelet matches the signal at that particular point in time. The better the fit, the higher the resulting transformed signal at that timepoint. For each frequency a different wavelet is constructed. This way the signal is broken down into its frequency components over time. The Gaussian taper ensures edge artefacts are diminished.

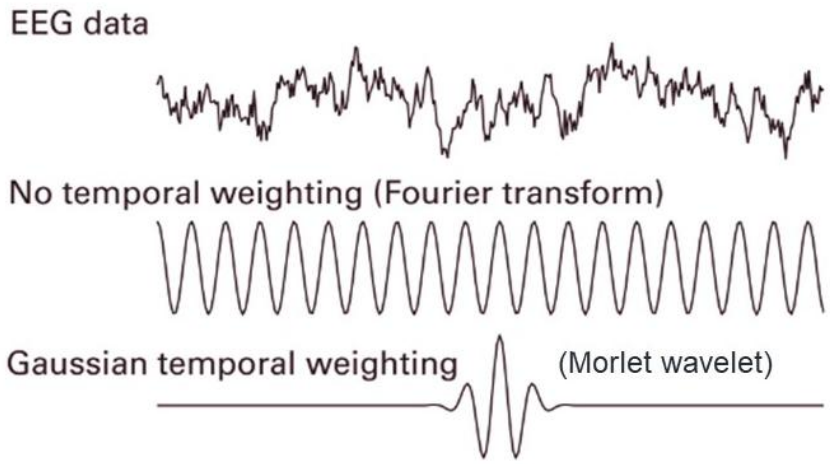

Figure 5.4 Morlet wavelet. Adapted from Cohen (2014).

In this study, TFRs were calculated using Morlet wavelets in time windows time-locked to stimulus onset of S1. Analyses were done in sleep stage N2, when K-complexes and sleep spindles are most abundant. Only artefact free segments were included. Morlet Wavelet analyses require setting multiple parameters which influence the data analysis: segment length, frequency range, bin width and number of wavelet cycles. The *segment length* needs to balance two opposing needs. On the one hand shorter segments are preferred to increase the number of segments to average, per participant. The longer the segments are, the higher the chance they will include artefacts and therefore be excluded. On the other hand, the length of the segment determines the *lower end of the frequency* spectrum that can be analysed. Cohen (2014) describes that several cycles of a frequency band should be present per segment to extract robust band-specific information. This means that to obtain accurate information, lower frequencies need longer segments than higher frequencies. We settled on 6 second long segments (from -1 to 5 seconds timelocked to S1), which still allows for the inclusion of frequencies of 2 Hz. The *higher end of the frequency range* in turn is limited by the sampling rate as there need to be sufficient datapoints per cycle to get a reliable estimate. In theory, according to the Nyquist-Shannon sampling theorem, with a sampling frequency of 500 Hz, the maximum frequency that could be reliably determined is 250 Hz. However, during sleep, the EEG signal is mostly composed of much lower frequencies. In addition, as a general rule of thumb, it is better to limit the range of frequencies to increase the statistical power. Including many frequencies requires performing multiple

statistical tests, which increases the risk of false positives due to multiple comparisons. The upper limit of the frequency range is therefore set to 30 Hz. Lastly, *the number of wavelet cycles* of the Gaussian taper, which determines the width of the wavelet has to be set. This parameter influences the temporal and frequency precisions of the signal. More cycles result in better temporal precision, but at the cost of frequency precision. Moreover, the right number of cycles depends on the frequency band. If a large range of frequencies are analysed at once, it may be beneficial to change the number of cycles of the wavelet accordingly, to avoid distortions. Cohen (2014) recommends a minimum of three cycles and a maximum of 14 cycles. In this study, the frequency range was 2-30 Hz in bins of 1 Hz, and we increased the number of cycles linearly from 3 to 14 Hz in the same number of steps as the frequencies.

In the segmented data, the power of the signal was computed in channel 'Cz' using Morlet wavelets via the time_frequency.tfr_morlet() function from the MNE package. Two recordings with noisy 'Cz' channels were excluded, resulting in 31 recordings for analysis. Next, the computed power was averaged across segments for each participant. On average, each participant had 50 artifact-free N2 segments (SD = 28, min = 14, max = 114). A baseline correction was then applied using a log ratio from -0.5 to -0.1 relative to the onset of S1, so the signal now represents the change in power relative to before stimulation. For a summary of the analyses steps see Fig. 5.5. To test whether there was a significant change in the power of any of the frequency bands after the stimulus compared to before, a one-sample t-test was run on the baselined power at each timepoint in the segment. To correct for multiple comparisons, a cluster-based permutation approach was used, which will be explained in detail in the following section.

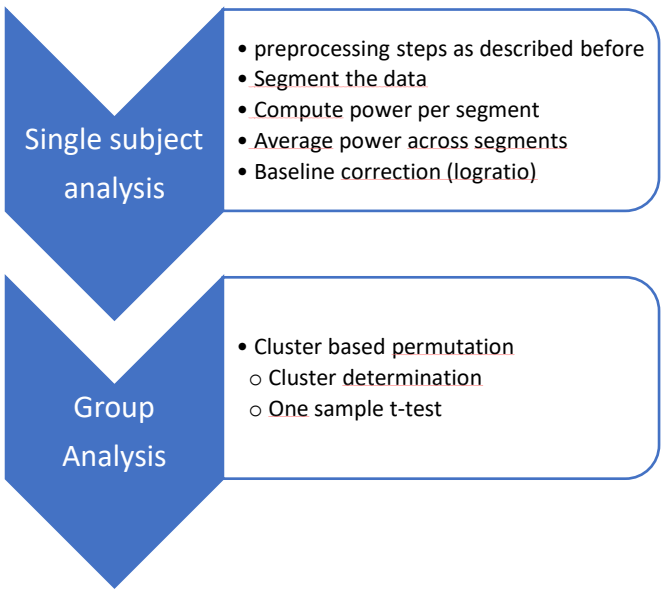

Figure 5.5 Summary of the analyses steps of time frequency representations

5.3.1.2.1 Statistical approach for TFR: cluster-based permutation

One of the challenges in the statistical analysis of TFR data is its three-dimensional nature. TFR data includes a large number of data points over time, across many frequency bands, and from multiple electrodes. The temporal resolution is determined by the sampling rate, and the number of electrodes depends on the EEG system used for data collection. When conducting significance testing to identify effects, this gives rise to the multiple comparison problem: the probability of finding false positives increases with the number of statistical tests performed, known as the family-wise error rate (FWER).

A common solution to this problem is reduce the dimensions by focusing on an area of interest and then taking an average across that area. This limits the amounts of significance tests that need to be conducted. While this might be an appropriate choice for a study interested in a well-established effect, such as N400 in language research, it is not an ideal approach for every study. This is a particular issue in developmental science because many well-known phenomena are established in studies using adult participants. In the developing brain, neural responses are often delayed as information processing takes longer (A. Chen et al., 2016), frequency ranges tend to shift to the slower side compared to adults (P. J. Marshall et al., 2002) and the topographical distribution changes as a result of anatomical and morphological changes in the brain (Ringli & Huber, 2011). Identifying an a-priori area of interest is therefore not always possible. In addition, averaging across multiple datapoints reduces the richness of the data.

One way to circumvent the multiple comparison problem and at the same time still preserving the richness of the data, is to use cluster-based permutation analysis. This is a method which was first used for MRI data (Bullmore et al., 1999), but was then expanded to EEG (Maris & Oostenveld, 2007). There are two parts to cluster-based permutation: 1. Cluster formation and 2. Permutation-based inference.

Cluster based permutation starts by performing a statistical test, for example between conditions or groups, on each datapoint. This results in a map of test statistics instead of raw data points. Usually, an observed test statistics would be compared to a t-distribution and if a p-value that exceeds the chosen alpha-level is found, that result is concluded to be likely different from zero. However as outlined above, the likelihood of false positives increases when statistical tests are repeated many times. To circumvent this issue, before making any inferences about the test statistics, clusters are formed within the data. The test scores are grouped into clusters, based on the assumption that true effects would show similar patterns in neighbouring datapoints. A real effect will not happen in just one isolated datapoint, but will rather be similar across spatially and or temporally adjacent datapoints. If an effect does occur in a singular point, then it is either an artefact or it might not be that meaningful from a biological standpoint. A key difference with choosing an area of interest a-

priori, is that this approach is completely data-driven. An algorithm is used to detect clusters of datapoints and each cluster gets assigned a summary value, for example by summing all test-statistics within a cluster. Due to the cluster formation, no statistical inferences will be made about individual datapoints. This has important conceptual implications, as it means that interpretations about temporal or spatial precision cannot be made. Instead the statistics will inform about the size of the cluster (Maris & Oostenveld, 2007; Sassenhagen & Draschkow, 2019). At this stage, a first threshold is set, the cluster threshold, that determines which datapoints are included in a cluster.

Next, statistical inferences are made from the cluster size based on a generated permutation distribution. This is done by repeating the cluster formation process many times, but each time the labels of condition or group are randomly assigned or 'permuted', hence the name cluster-based permutation. Each permutation produces a test statistic from the largest cluster found in the data. These cluster test statistics are used to generate the permutation distribution, which surrogates as a null distribution. The test statistic of the observed data is then compared to the permutation distribution. In case of an alpha level of 0.05, an effect in the observed data is considered significant if the test statistic of the cluster only occurred in less than 5% of the permutations. In theory, the more permutation one uses to build the permutation distribution, the better. However, as this can be quite time-consuming, the permutation distribution tends to be approximated by a Monte Carlo estimate. A rule of thumb is that at least 1000 permutations should be run (Meyer et al., 2021).

It is important to highlight again that this approach does not formally establish the onset or offset of a cluster (e.g. latency of the effect). It only informs us whether the size of an observed cluster is significantly different to other cluster sizes when the data is randomly rearranged. This is because the clusters group similar test statistics, however, it is not formally tested whether a point on the edge of the cluster should or should not be included (Sassenhagen & Draschkow, 2019).

Cluster-based permutation offers several key advantages. Firstly, it is a non-parametric method, so it does not rely on assumptions about the normality of the data, because the permutation distribution can take on any shape. Secondly, it can be used as a correction method for multiple comparisons on any statistical test, whether it be t-tests, ANOVAs or correlations. Thirdly, cluster-based permutation testing does not require the identification of a priori regions of interest, particularity interesting for developmental data.

Settings

In this study, a two-tailed, one sample t-test was used to determine whether the log ratios were different from zero, using the function *mne.stats.permutation_cluster_1samp_test()*. A cluster threshold of 0.05 was set to define clusters, quantified by summing values within each cluster. The

permutation distribution was generated by randomly shuffling the signs of the log ratios for each participant over 10,000 iterations. Clusters were considered significant at $p < 0.05$.

5.3.1.3 Elicited events

Event-likelihood, sleep spindles and K-complexes, is compared in stimulus ON and stimulus OFF windows. A higher likelihood of events in the stimulus ON window than OFF, would indicate that stimulation evokes these events. The effect of LT scores on event likelihood will also be explored, as well as the interaction with ON/OFF windows. The latter will inform about whether LT scores impact the evoked responses to stimulation in particular rather than the spontaneous presentation of these events. Again, two recordings were removed that had a noisy Cz channel, as well as two participants with missing data on the LT questionnaire, leaving 29 recordings for these analyses.

5.3.1.3.1 K-complex likelihood

K-complex detection was performed with the automated slow wave detection algorithm by YASA (See details in Chapter 4). For this analysis, artefact-free N2 segments were created starting 4.15 seconds before S1 and ending 12.35 sec after S1 onset. A K-complex was counted in response to S1 if the negative peak fell in a window 450-700 ms from S1 onset (stimulus ON window). Because of a refractory period after an evoked K-complex (Campbell, 2010), only the response to S1 is presented here but see Appendix E for measures of K-complex likelihood after both S1 and S2. K-complexes were also counted in a stimulus OFF window of the same length at -1250 to -1000 ms time-locked to S1 onset (See fig. 5.6). Although the OFF-window is consistently 1250 ms before S1 onset, it is jittered in comparison to the previous stimulus, as the interstimulus interval varied between 12 and 18 sec (see fig. 5.2). It is therefore unlikely that there are any confounding anticipatory effects which would influence the event count in the OFF window. From these counts, the likelihood of a K-complex was calculated by dividing the total number of K-complexes in each window (ON or OFF) by the number of stimuli. On average there were 41 stimuli per recording in artefact-free N2. The number ranged from 11 to 92.

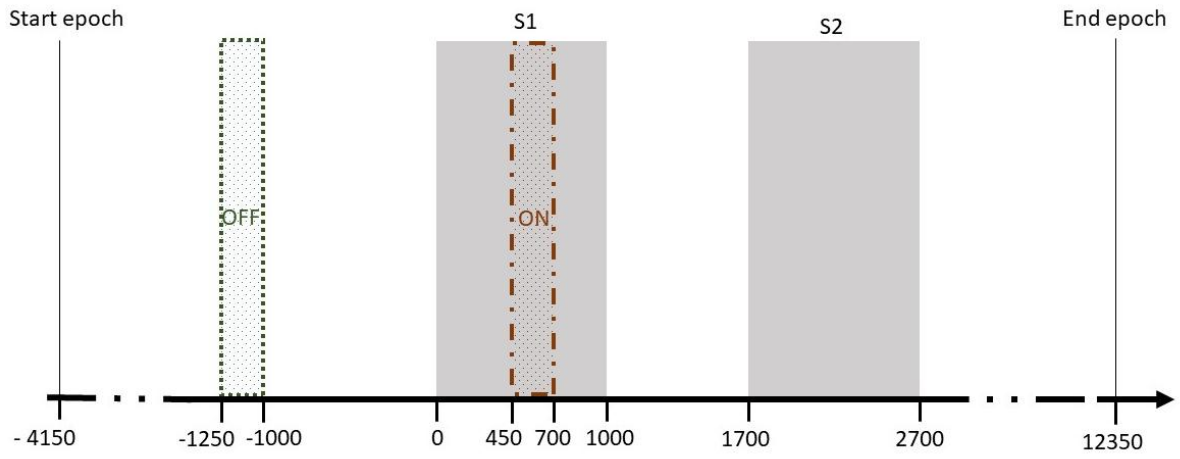

Figure 5.6 Analysis window used for K-complex likelihood.

5.3.1.3.2 Sleep spindle likelihood

Sleep spindles were detected automatically in sleep stage N2 in channel Cz, using *Yet Another Spindle Algorithm* (YASA). Details on the parameters and justification of those parameters are described in detail below in section 5.4.1 and in Chapter 4. While the (adult) literature is clear about the timings of an evoked K-complex, there is much less clarity about the timings of evoked sleep spindles and even whether sleep spindles are evoked by stimulation all together. We therefore choose a longer time window for the detection of sleep spindles that spanned over both S1 and S2.

Artefact free N2 segments of 8.8 sec were selected, from -4.4 to +4.4 from S1 onset. This allowed for a buffer zone of 1 sec at each end of the segment to avoid interference of edge artefacts with sleep spindle detection. Sleep spindles were counted in response to the stimulation if they started between 0 and 3.4 seconds after S1 onset, called the ON window. Sleep spindles in the control window were counted if they started at -3.4 to 0 seconds before S1 onset, called the OFF window (See Fig. 5.7). From these counts, the likelihood of a sleep spindles was calculated by dividing the total number of sleep spindles per recording by the number of stimuli. On average there were 48 of stimuli per recording in artefact-free N2. The number ranged from 14 to 108.

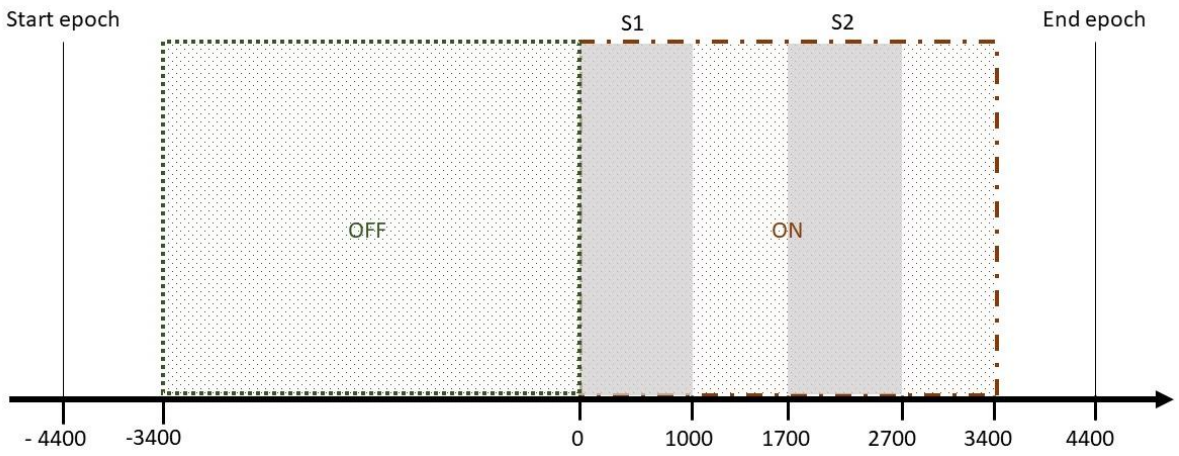

Figure 5.7 Analysis window used for sleep spindle likelihood.

5.3.1.3.3 Statistical approach for elicited events

Justification for using linear mixed models

In this section, stimulation is represented by the absence or presence of auditory stimulation in stimulus OFF vs stimulus ON windows, coded as 0 or 1 respectively. The simplest statistical approach would be to use general linear models, such as a multiple linear regression, with stimulus and LT as predictor variables and the micro- and macro-sleep measures of interest as outcome variables. This also allows for additional co-variates to be added, such as age and sex. However, the study design violates the independence assumption, as some variables are measured twice within the same participants. A common approach when the independence assumption is violated is to run a repeated measures ANOVA. However, an ANOVA does not allow any incompleteness of data. Additionally, no covariates can be added. In the second chapter, we used a marginal model, GEE, to account for the dependence between measures. In this chapter we will use a mixed effect model. A key difference between the two is the way the correlations between repeated measures are accounted for. In marginal models, a working correlation matrix is specified, which accounts for the dependence between measures, but treats it as a 'nuisance'. The results of marginal models, do not include any information about the individual variability. Mixed effect models on the other hand explicitly model individual variability, through the inclusion of 'random effects'. While the working correlation matrix in marginal models is the same across all subjects, the random effect allows the dependency to differ for each subject. To better account for the within person variation in the sample, mixed effect models are used here.

Mixed effects models are called 'mixed', because they combine fixed and random effects. Fixed effects model average trends across the entire sample, while random effects capture the subject-specific deviations from the average trend. If a random effect variance is zero, this indicates that there is no

subject specific variation. Random effects can either allow for differences in the intercept, slope or both. However, when there are only two measurements per subject, as in our study design, it is not possible to estimate random slopes because there are no residuals from a line connecting two points. We therefore only specify a random intercept in these models.

Linear mixed effect models (LMM) assume that the residuals of the model are normally distributed. For non-normal or non-continuous data, generalized mixed effect model can be used instead (GMM). Evaluating significance in LMMs is not straightforward, as, unlike general linear models, the output of LMMs does not provide a p-value for each effect within the model. This is because the denominator degrees of freedom are ambiguous in multilevel models (Baayen et al., 2008). E.g. Should the degrees of freedom be derived from the number of observations (level 1), the number of subjects (level 2) or a combination of both? However, an estimate of the degrees of freedom is needed to calculate a p-value from t- and F-statistics. Two common methods to evaluate significance of effects in LMMs are likelihood ratio tests and the t-as-z approach. Both these methods are sensitive to sample size, with higher Type 1 error rates for smaller sample sizes, and are not recommended when the number of participants is < 50. For smaller sample sizes, the Satterthwaite approximation for degrees of freedom can be used. This method is considered more robust to different sample sizes, because it produces similar Type I errors across sample sizes (Luke, 2017). Therefore in this study, the estimates and t-statistics of model parameters are obtained using the maximum likelihood method, followed by the Satterthwaite approximation to obtain df and p-values for each fixed effect in the model.

LMMs were run with stimulus, LT, sex and age as fixed main effects and the individuals as random intercept (See equation 5.1a). In a next step, the interaction effect between stimulus and LT was added (equation 5.1b). Sensitivity analysis followed by adding autism-likelihood status as a covariate (equation 5.2). This approach and the choice of covariates are based on the preregistered analyses (see more detail 5.4.1.2). LMM were performed with the R-package lmerTest (Kuznetsova et al., 2017).

Equation 5.1 Linear mixed effect models. The base model (a) includes the main effects only, the interaction model (b) includes the interaction term. Event likelihood is either K-complex or sleep spindle likelihood. LT = Low threshold.

$$Event\ likelihood \sim Stimulus\ (0FF\ vs\ ON) + LT + Sex + Age + (1|subject) \quad \text{(a)}$$

$$Event\ likelihood \sim Stimulus\ (OFF\ vs\ ON) + LT + Sex + Age + \boldsymbol{Stimulus * LT} + (1|subject) \quad \text{(b)}$$

Equation 5.2 Sensitivity analysis including ASD-likelihood status coded as 0 (TL) and 1 (EL) to the base model (a) and interaction model (b).

$$y \sim Stimulus + LT + Sex + Age + \boldsymbol{ASDlikelihood} + (1|subject) \quad \text{(a)}$$

$$y \sim Stimulus + LT + Sex + Age + \boldsymbol{ASDlikelihood} + Condition * LT + (1|subject) \quad \text{(b)}$$

5.3.2 Results of time-locked responses

5.3.2.1 ERPs

ERPs were plotted to visually assess whether stimulation was registered during NREM sleep in the central channels (Fig. 5.8). A clear response can be seen after onset of S1 and S2. No further analysis was carried out on the ERPs.

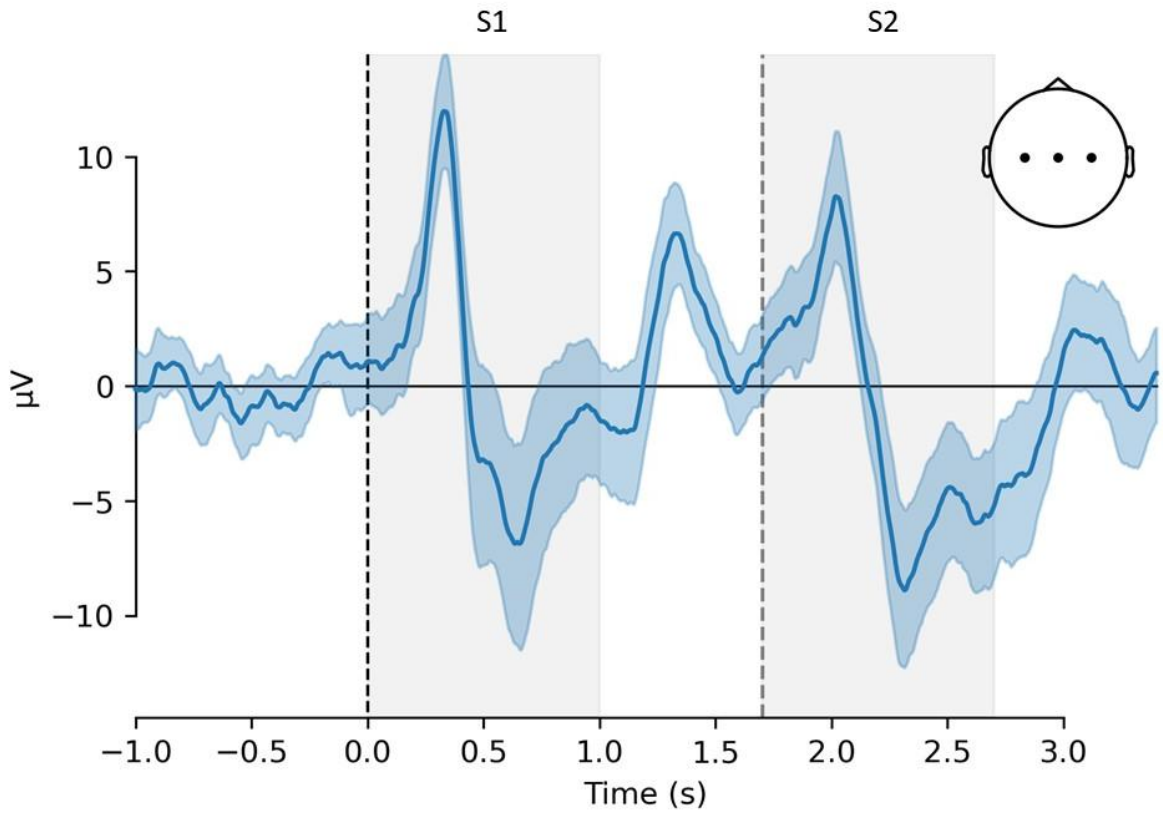

Figure 5.8 Event Related Potentials in the central channels (C3, Cz and C4). Onset of S1 and S2 are demarcated by the dotted vertical lines. Shaded areas indicated the duration of the stimuli. Baseline correction was applied from -1 – 0 from S1 onset.

5.3.2.2 TFR

Cluster based permutation

The cluster-based permutation test detected 31 clusters in the data, of which the size of two clusters was significant or marginally significant after comparison to the permutation distribution (See fig. 5.9).

A positive cluster was found that approached significance (p = .067) with a two-tailed test, but reached significance with a one-tailed test (p= .047). The positive cluster was located at the lower end of the frequency spectrum, in the delta and low theta band, approximately between 0 and 1000 ms after the onset of S1. A significant negative cluster was found, with a probability of 0.047 in the permutation distribution, indicating a decrease in power compared to the baseline activity. The negative cluster spanned over the sigma band and started around the onset of S2. This leads us to conclude that on average, infants tended to register the stimuli, as activity before and after the stimulus was significantly different. We continue these analyses by exploring whether the increase in low frequency activity corresponds to an increase in K-complex occurrence and whether the decrease in the sigma band reflects altered sleep spindle production.

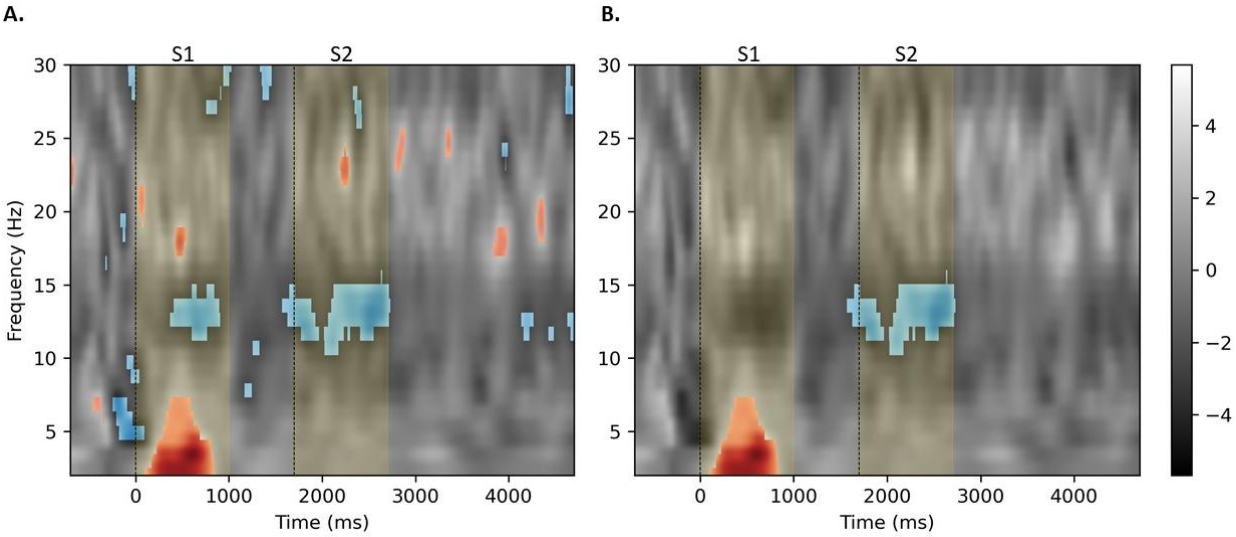

Figure 5.9 TFR cluster-based permutation. Dashed black vertical lines are the stimulus onsets of S1 and S2. The shaded yellow area is the duration of the stimuli. ***A.*** *All detected clusters before permutation.* ***B.*** *Clusters that have a p-value < 0.1 after permutation.*

5.3.2.3 Elicited events

K-complex likelihood

The LMM of K-complex likelihood resulted in a singular fit, likely because there was almost no within person variance in K-complex likelihood. A multiple linear regression was therefore run, without the random effect of individual. The OFF/ON window significantly predicted K-complex likelihood, with more K-complexes in the window after S1 than before S1 (Est. 4.37, p=0.017; see fig 5.10A). LT also predicted the likelihood of a K-complex occurring, with infants that score high on LT (more sensitive to sensory stimulation) having a lower likelihood of K-complexes, irrespective of the presence or absence of stimulation (Est. = -5.35, p = 0.035; see fig 5.10B). There was no interaction effect of LT and the

OFF/ON window (Est. = 3.02, p = 0.544). The results did not change when autism-likelihood was added as a covariate.

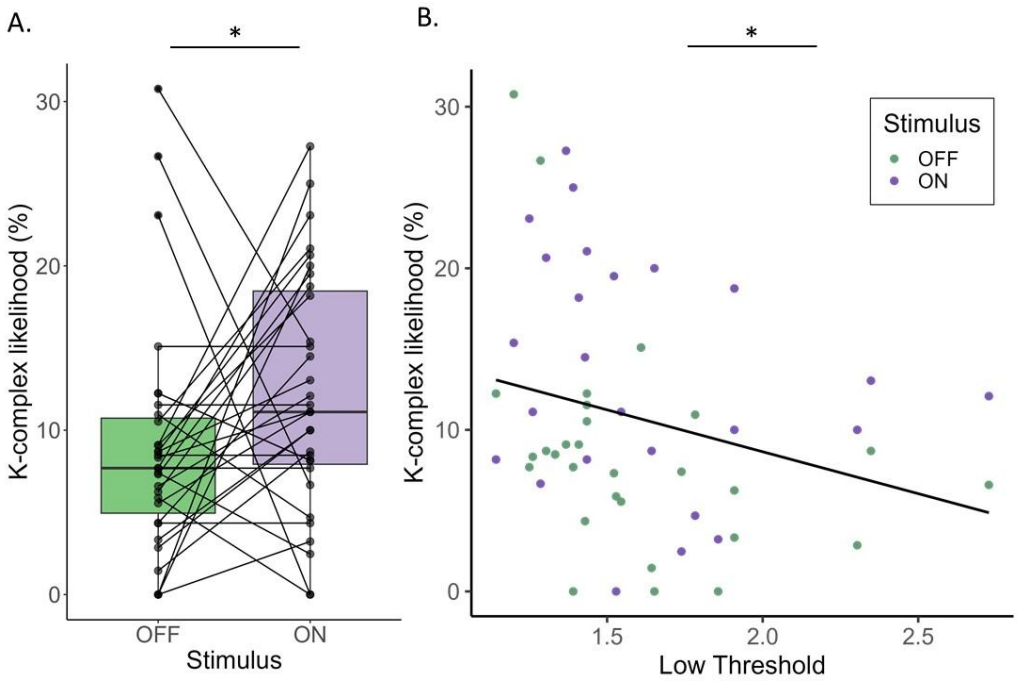

Figure 5.10 K-complex likelihood results. ***A.*** *K-complexes increase significantly in response to stimulation.* ***B.*** *Association between K-complex likelihood and low threshold; higher LT values correspond to higher sensory sensitivity.*

Sleep spindle likelihood

Sleep spindle likelihood did not differ significantly in windows with (ON) or without (OFF) stimulation (Est = -0.91, p=0.313; see fig 5.11A). LT did not have a significant effect on sleep spindle likelihood (Est. = 3.69, p = 0.153; see fig. 5.11B), nor did the interaction between LT and OFF/ON windows (Est. = -0.23, p = 0.927). The results did not change when autism-likelihood was added as a covariate.

To summarise, after an auditory stimulus, the power of oscillations in the lower end of the spectrum (theta and delta range) increases compared to before the stimulus. This is likely due to evoked K-complexes. Indeed, the likelihood of a detected K-complex is higher after the stimulus than before. The likelihood of a K-complex occurring is significantly lower in infants that score high on LT, but is not related to whether a stimulus was presented. Although there was a significant decrease in the sigma range in the window after stimulation compared to before, this was not reflected in detected sleep spindles. There was no significant decrease in sleep spindle likelihood after stimulation, nor did LT predict the likelihood of a sleep spindle occurring.

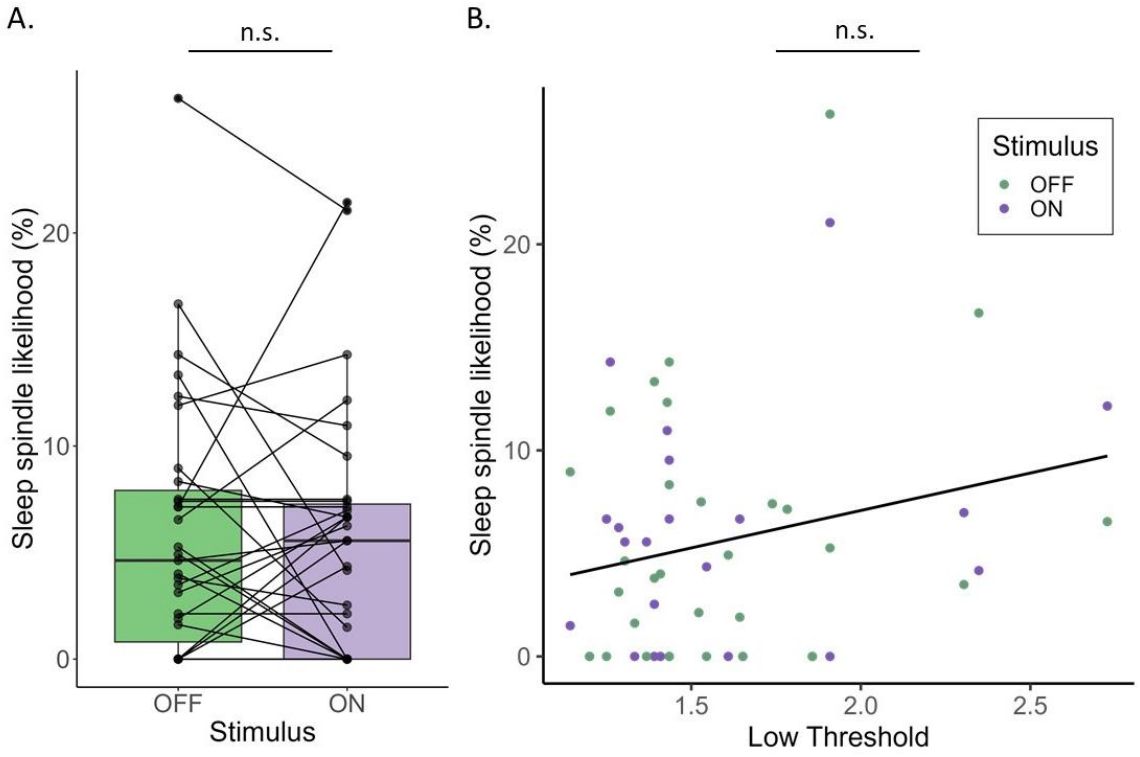

Figure 5.11 Sleep spindle likelihood results. ***A.*** *Sleep spindle likelihood (%) before (OFF) and after (ON) stimulation is not significantly different.* ***B.*** *Sleep spindle likelihood is not significantly associated with an infant's low threshold score.*

5.4 Pre-registered analyses: comparison of the Baseline vs. Stimulation naps

The second part of these analyses are pre-registered on the Open Science Framework (see link). A few changes were made to the pre-registered analyses. First, sex and age were added to all models as covariates. Second, all analyses with sleep spindles were performed in N2 only rather than in the combination of N2 and N3, because very few spindles were detected in N3. Using N2/N3 would have therefore reflected the proportions of N2/N3 for the variable sleep spindle density rather than how closely sleep spindles were spaced in time. Other deviations to the preregistration will be highlighted throughout. To justify regions of interest, some preliminary descriptive analyses were performed on the first 14 recordings.

5.4.1 Methods

5.4.1.1 Measures

5.4.1.1.1 Spindle detection

Sleep spindles were detected in channels F3, Fz, F4, FC1, FC2, C3, Cz, C4. The region of interest was based on topography of sleep spindle activity in 5-6-months-old infants (Sokoloff et al., 2021).

Topography plots in the pilot sample confirmed a similar topography in our sample of 8-11 month old infants (see Appendix D Fig. A.1). Automatic sleep spindle detection was performed as described in Chapter 4. We chose not to separate slow and fast spindles, because previous literature suggests two separate frequency peaks emerge from 18 months onwards, but are indistinguishable before that (Kwon et al., 2023). Preliminary analysis of 14 recordings confirmed that there was no markedly different topography of slow (9-13 Hz) and fast (13-16 Hz) sigma power across N2 and N3 (Appendix D Fig. A.2). Nor did we see two distinct sigma peaks in the individual power spectrum densities of F-, C- and P-channels (Appendix D. Fig. A.3). The YASA algorithm detects spindles based on three additional thresholds: Root mean square (rms), Relative power and correlation. The choice of these thresholds differs slightly from the pre-registration, as a more meticulous threshold determination was performed on a larger sample (see Chapter 4). The thresholds were set as follows: rms = 1.275, relative power = 0.13, correlation = 0.52.

5.4.1.1.2 Sigma power

In addition to sleep spindle density, sigma power (9-16 Hz) was in calculated in N2. Absolute power was calculated using Welch's method and a Hann window with a length of 4 sec. Median sigma activity was calculated in the same channels of interest as sleep spindles.

5.4.1.1.3 Slow wave activity

Slow waves are measured as slow wave activity in sleep stage N3, when slow waves are most prominent. A frequency band of 0.5-2 Hz was used. The absolute power spectral density was calculated using Welch's method and a Hann window with a length of 4 sec. The median was used when averaging periodograms. Next, SWA was averaged, using the median, across the following electrodes: F3, Fz, F4, FC1, FC2, C3, Cz, C4, O1, Oz and O2. This region of interest was selected based on Sokoloff et al. (2021), and confirmed in the subset of recordings (see Appendix D Fig. A.1).

5.4.1.1.4 Arousals and EEG activation

Arousals are measured in two ways, a discrete measure – arousal density (i.e. number of arousal divided by the time asleep) and a continuous measure of arousal – the activation index (AI). The latter was not pre-registered and added as an exploratory analysis.

Arousals were visually identified based on guidelines from the International Paediatric Work Group On Arousals (The International Paediatric Work Group On Arousals, 2005) and The Pediatric Task Force (Grigg-Damberger Madeleine et al., 2007). An arousal is scored if a change in activity lasts for more than 3 seconds, provided that baseline sleep has been established for at least 30 seconds prior to the arousal. To count as separate events, arousals have to be spaced by at least 10 seconds. An arousal can

lead to an awakening if it lasts for more than 30 seconds. Thus, the total number of arousals during sleep also incorporates the number of awakenings, as an awakening is an extension of an arousal.

The paediatric workgroup further divides arousals in subcortical arousals or cortical arousals, however both are combined in this study because differences in arousal thresholds are not the focus of this study. Due to the absence of equipment measuring heart rate or breathing patterns, an arousal was defined when two of the following criteria were present:

- A gross body movement detected by movement sensors or seen as movement artefacts in the somatic channels (ECG, EEG, respiratory parameters) or by observation.
- An increase in chin EMG amplitude, unless associated with sucking, that was not previously present.

Or for cortical arousals

- Abrupt change in EEG background frequency (of at least 1 Hz) for a min of 3 sec

Arousal density was measured as the total number of arousals (subcortical and cortical) divided by total sleep period (sleep onset – sleep offset) without arousal time. Arousals were excluded if they were caused by a known external factor, other than the auditory stimulation, such as the caregiver moving the baby. Arousals were not scored in 10 recordings, due to bad quality chin electrodes.

The second measure is the activation index (AI), which was calculated as the logarithm (base 10) of the power in the beta range (18-30 Hz) divided by the power in the delta range (0.5-4 Hz). This measure is based on two recent papers, one in mice (Cardis et al., 2021) and one in humans (Lecci et al., 2020). Because infants manifest slower rhythms than adults, the lower bound of the delta range was set at 0.5 instead of 1 Hz as in Lecci et al.'s study. Similar to Lecci et al., the AI was calculated in N2 and N3 separately. Visually detected arousals were excluded due to the interference of movement artefacts. Lecci et al. found a maximum effect of at Cz, which we therefore also used. The bandpower was calculated using the Welch method with a Hanning window and median as average across windows. Regarding the interpretation of the AI: recall that the logarithm of a division is equivalent to the subtraction of the log of the denominator from the log of the numerator (see equation 5.3). Delta power tends to have larger values than beta power, and the resulting AI will therefore be a negative value. The smaller the difference between beta and delta power, and thus the smaller the absolute value of AI, the more 'aroused' the brain is, as a large amount of beta compared to delta is assumed to represent a more awake brain. The larger the difference between beta and delta power, and thus the more negative the AI, the more 'asleep' the brain is assumed to be.

Equation 5.3 Activation index.

$$log_{10}\frac{beta}{delta} = log_{10}(beta) - log_{10}(delta)$$

5.4.1.2 Statistical approach

Similar to the statistical approach of the time-locked analyses, stimulation is characterised as a binary variable. In this part, the stimulation is represented by the absence or presence of auditory stimulation across a whole nap.

Analysis steps and model specification

As a first step, the distribution of the variables was checked for the presence of outliers. Similar to the previous chapters, outliers were defined as any value that had a z-score above 3. Any outlier above 4 SD was Winsorized. Values between 3 and 4 SD were visually checked on a scatterplot in relation to other variables. See Appendix G for a table with all datapoints that were above 3 SD. As a result, two values for sleep spindle density in N2 (1 EL, 1 TL), one value for median sleep spindle frequency (TL) and one value for arousal density (TL) were Winsorized.

The main analyses focus on sleep micro-architecture and are split into two parts, variables related to sleep protection and to sleep disruption. Before the main analyses, preliminary analyses were run to see whether stimulation affected sleep macro-architecture. A simple mixed model was run to assess the effects of condition on sleep macro-architecture whilst accounting for within-person effects (see equation 5.4). Separate models were run for nap duration and sleep stage distribution. The latter is the proportion of the nap spent in each sleep stage. Although the pre-registration states that a GMM with a logit link function and quasi-binomial distribution would be used (because it is a proportion variable), using a quasi-binomial distribution was possible in R-package lmerTest only for generalized linear models. Therefore a LMM was run for sleep stage proportion, but that resulted in a 'singular fit'. A singular model fit happens when the random effect variance is close to zero. This means that there is no person-specific variance in the proportion of sleep stages. A generalized linear model was eventually run with a logit link function and quasi-binomial distribution. For nap duration a LMM was run. Contrary to the pre-registration, analysis with wake after sleep onset (WASO) as an outcome variable was not included, because 65% of the recordings did not have wake periods during the nap.

Equation 5.4 Linear mixed effect model to test differences in macro-architecture variables (y).

$$y \sim Condition + \ (1|subject)$$

For the main analyses, LMM were run separately for all outcome variables of interest: SWA, sleep spindle density and arousal density. Given the increased interest in the literature, we will also report on the activation index. Studies often also report on other spindle characteristics such as sleep spindle duration, frequency and absolute power; these were added as exploratory analyses. Based on the results from the time-locked analyses, which showed a decrease in sigma activity after stimulation, sigma power was also added as an outcome variable as exploratory analysis. The fixed effects were nap condition (baseline = 0; stimulation = 1), LT, sex and age. In the pre-registered analyses, sex was to be included only if the preliminary analysis indicated significant sex differences based on a t-test. However, we decided to err on the side of caution and add sex to all models, as some variables showed marginally significant differences between sexes. In the model with arousal density as an outcome variable, sleep position (whether the infant was sleeping on the caregiver or alone) was added as control variable. In all models, participants were added as a random intercept. First the models were run with the main effects only (Equation 5.5a), then the interaction effect between condition and LT was added (equation 5.5b). Estimates and significance values for the main effects were taken from the first model, while those for the interaction effect was taken from the second. As a sensitivity check, autism likelihood status was added as a control variable to the models (See equations 5.6a and 5.6b), instead of removing EL-ASD participants as pre-registered. The former approach was preferred over the latter, to maximise sample size. Although not all continuous outcome variables were normally distributed, LMMs were used because they are fairly robust to non-normality (Schielzeth et al., 2020).

Equation 5.5 Linear Mixed Effect Model. Base model includes the main effects (1), interaction model includes the interaction term (2). y = sleep variable of interest, LT = Low Threshold

$$y \sim Condition + LT + Sex + Age + \ (1|subject) \quad \text{(a)}$$

$$y \sim Condition + LT + Sex + Age + \ \boldsymbol{Condition * LT} + \ (1|subject) \quad \text{(b)}$$

Equation 5.6 Sensitivity analyses. ASD-likelihood status is added to the base model (1) as well as the interaction model (2).

$$y \sim Condition + LT + Sex + Age + \ \boldsymbol{ASDlikelihood} + \ (1|subject) \quad \text{(a)}$$

$$y \sim Condition + LT + Sex + Age + \boldsymbol{ASDlikelihood} + \ Condition * LT + \ (1|subject) \quad \text{(b)}$$

5.4.2 Results of pre-registered analyses

Table 5.1 Descriptives per condition. Sleep Onset Latency was measured as the time from the lights off moment to the start of first epoch of sleep (including N1). Sleep efficiency is calculated as the total sleep time (N1 + N2 + N3 + REM) divided by the duration from the first to last period of sleep. Mean (SD). V = visit; M=male; F=female.

	Baseline	Stimulation
N	38	34
M:F	21:17	17:17
EL:TL	7:31	7:27
V1:V2	22:16	19:15
Age (in days)	303 (34)	300 (32)
Sleep Macro-architecture		
Sleep onset latency (min)	10.3 (6.6)	11.5 (7.2)
Nap duration (min)	62.2 (23.5)	50.9 (16.7)
Wake After Sleep Onset (min)	0.9 (1.6)	0.6 (1.6)
Sleep efficiency (%)	96.9 (3.7)	97.5 (3.1)
Sleep stages		
N1 (min)	12.1 (9.7)	10.0 (4.6)
N2 (min)	21.5 (11.4)	17.1 (10.4)
N3 (min)	20.8 (9.1)	20.8 (8.4)
REM (min)	5.8 (6.7)	4.1 (5.9)

A total 41 participants and 71 nap recordings contributed to at least one of the analyses. The exact sample sizes are stated per analysis. Sex, autism likelihood status, visit and age were not significantly different in the two conditions (See table 5.1). All outcome measures, except sleep spindle density and - power, showed high within-person stability across the two naps ($r > 0.5$, table 5.2).

Table 5.2 Pearson correlations between repeated measures. AI = Activation index, SWA = Slow wave activity

	Pearson's r	p-value
Arousal density	0.541	**0.004**
AI N2	0.753	**<0.001**
AI N3	0.624	**<0.001**
SWA N3	0.842	**<0.001**
Sleep spindles N2		
density	0.095	0.674
abs power	0.378	0.083
frequency	0.896	**<0.001**
duration	0.723	**<0.001**

5.4.2.1 Macro-architecture

On average, infants slept 60.2 ± 23.5 min in the baseline condition and 50.9 ± 16.7 min in the stimulation condition (Fig. 5.12B). Stimulation significantly affected the duration of the nap, so that infants napped shorter in the stimulation compared to baseline condition (Est. = -11.7, p = 0.018). As

expected, there was a significant effect of sleep stage on the proportion of time in the nap (Est. = -0.17, p < 0.001), indicating that different sleep stages had varying proportions of the nap. There was no significant interaction effect between condition and the proportion of sleep stages (Est. = -0.04, p = 0.705, Fig 5.12A), meaning that the distribution of sleep stages was not significantly different between the baseline and stimulation nap.

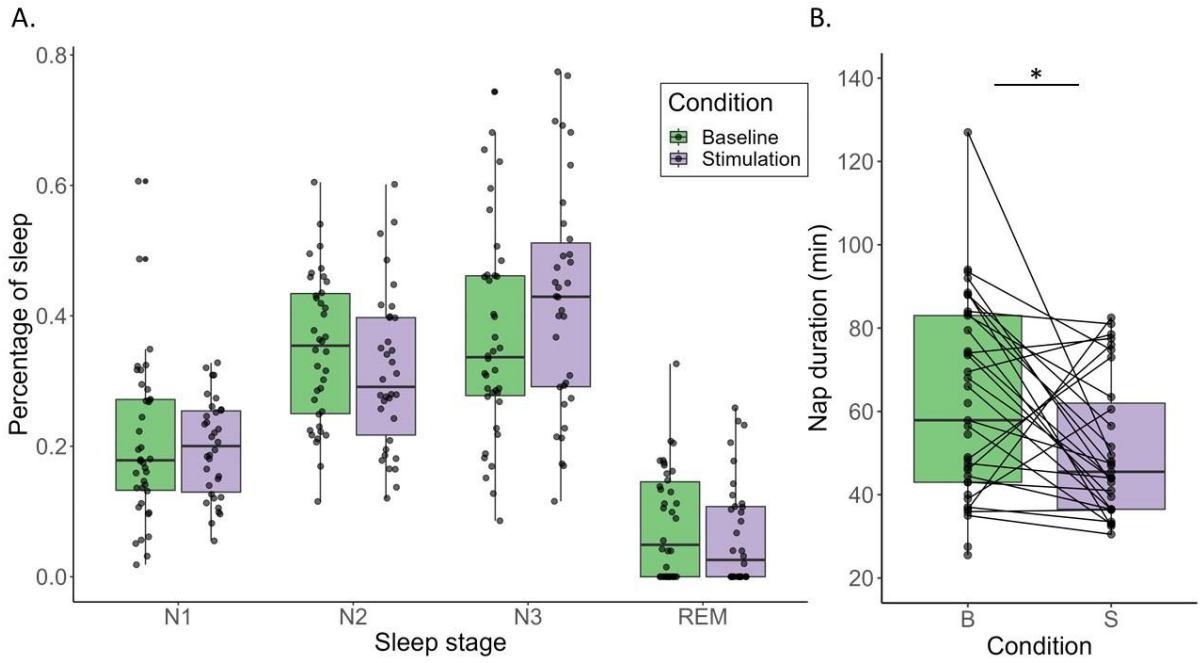

Figure 5.12 Differences in sleep macro-architecture between the baseline (green) and stimulation (purple) nap. ***A.*** *Percentage of the nap spent in each sleep stage. There were no significant differences in sleep stage proportions across the two naps.* ***B.*** *The duration of the naps. Infants spent significantly less time asleep in the stimulation nap compared to the baseline nap (p=0.018).*

5.4.2.2 Sleep protection

SWA

The power of the slow waves in N3 was not significantly different between the baseline and stimulation nap. (Est. = -61, p = 0.449, see fig. 5.13A). LT scores significantly predicted SWA, irrespective of the condition, such that higher LT scores associated with lower SWA (Est.= -629, p = 0.029, see fig. 5.13B). However, there was no significant interaction effect between LT and condition (Est. = -18, p = 0.930), indicating that infants that score higher on LT tend to have lower SWA, regardless of the sensory environment. See results summarized in table 5.3. Results remained similar when controlling for autism likelihood status.

Table 5.3 Results from linear mixed effect model with slow wave activity (SWA) as the outcome variable. SE = Standard Error; LT = Low Threshold. Number of recordings = 58, Number of participants= 35.

Predictors	**Estimate**	**SE**	**t**	**p**
Condition	-60.94	79.20	-0.769	0.449
LT	-628.62	276.15	-2.276	**0.029***
Sex (0=M, 1=F)	-362.30	216.70	-1.672	0.103
Age	1.635	2.77	0.589	0.558
LT*Condition	-18.15	203.49	-0.089	0.930

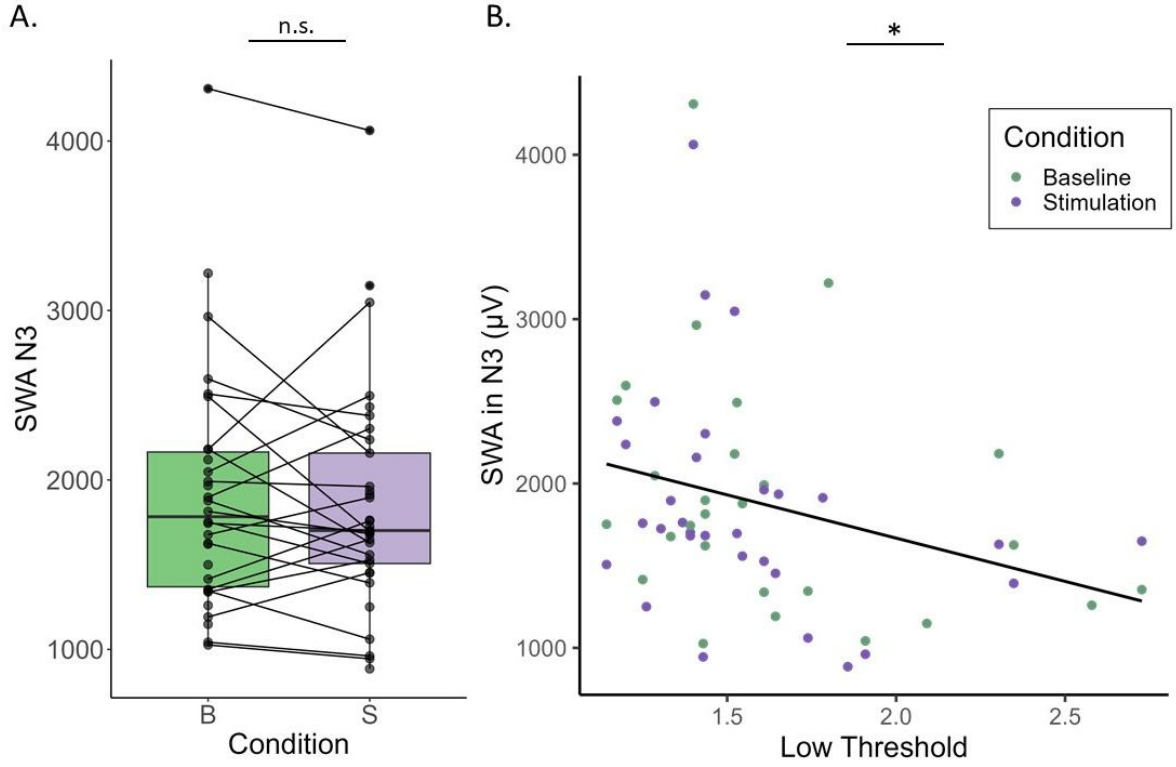

Figure 5.13 A. Slow Wave Activity (SWA) in baseline (B) and stimulation (S) conditions in sleep stage N3. B. Association between SWA and low threshold.

Sleep spindle features

Sleep spindle density in N2 was not significantly different between the baseline and stimulation nap (Est. = -0.19, p = 0.308). There was no significant main effect of LT on sleep spindle density (Est. = 0.44, p = 0.100). However, when there was stimulation, infants that scored higher on LT, showed a reduction in sleep spindle density compared to the baseline nap (Est. = -1.27, p = 0.004, see fig 5.14A). Adding autism likelihood status to the model did not change the results. To confirm whether these differences are also reflects in sigma power and given the significant decrease in sigma power after stimulation (See section 5.3.2.2), we ran an exploratory analysis on sigma power in N2. There was no significant difference in ***sigma power*** between the baseline and stimulation nap (Est. = 0.89, p = 0.583), nor was

there a significant main effect of LT on sigma power (Est. = 1.15, p = 0.623). In contrast to sleep spindle density, there was no significant interaction effect between nap condition and LT scores Est. = -3.22, p = 0.436). The results remained similar, when autism likelihood status was added to the model. Results of both models summarised in table 5.4

Table 5.4 Results from linear mixed effect models with sleep spindle density and sigma activity in sleep stage N2 as the outcome variable. For sleep spindle density there were 57 recordings of 35 participants. For Sigma activity there were 58 nap recordings from 35 different participants. SE = Standard Error; Est = Estimate; LT = Low Threshold.

	Sleep spindle density				**Sigma activity**			
Predictors	**Est.**	**SE**	**t**	**p**	**Est.**	**SE**	**t**	**p**
Condition	-0.189	0.182	-1.039	0.308	0.890	1.605	0.554	0.583
LT	0.439	0.258	1.701	0.100	1.150	2.317	0.496	0.623
Sex (0=M, 1=F)	0.237	0.204	1.158	0.257	0.591	1.830	0.323	0.749
Age	0.003	0.003	0.791	0.434	0.024	0.030	0.802	0.427
LT*Condition	-1.267	0.394	3.218	**0.004**	-3.219	4.083	-0.788	0.436

As additional exploratory analyses, three more models were run with sleep spindle frequency, duration and absolute power as outcome variables (see table 5.5). The condition had a significant effect on sleep spindle frequency, with lower frequency sleep spindles in the stimulation condition (Est. = -0.11, p = 0.050), but not on the duration (Est. = 0.01, p = 0.806) or power (Est. = 0.08, p=0.241). LT did not significantly predict any of the sleep spindle features (frequency: Est. = -0.03, p = 0.922; duration: Est. 0.11, p = 0.087; power: Est.< -0.01, p = 0.987). However, the interaction between LT and condition was significant for sleep spindle duration (Est.= -0.15, p=0.017, see fig 5.14B). Individuals with high scores on LT had significantly shorter sleep spindles during the stimulation nap compared to the baseline nap. This finding is in line with what was reported for sleep spindle density as density and median sleep spindle duration are inversely correlated (r = 0.714, p < 0.001). All results were similar after controlling for autism likelihood.

Table 5.5 Results from linear mixed effect models with Sleep spindle frequency, duration and absolute power in sleep stage N2 as the outcome variables. Number of recordings = 57, Number of participants= 35. SE = Standard Error; LT = Low Threshold.

	Frequency		Duration		Absolute power	
Predictors	**Estimate**	**p**	**Estimate**	**p**	**Estimate**	**p**
Condition	-0.114	**0.050***	0.006	0.806	0.083	0.241
LT	-0.025	0.922	0.110	0.087	-0.002	0.987
Sex (0=M, 1=F)	0.403	**0.048***	0.061	0.221	0.128	0.139
Age	-0.001	0.5503	-0.0002	0.743	0.002	0.274
LT*Condition	0.000	0.559	-0.147	**0.017***	-0.174	0.326

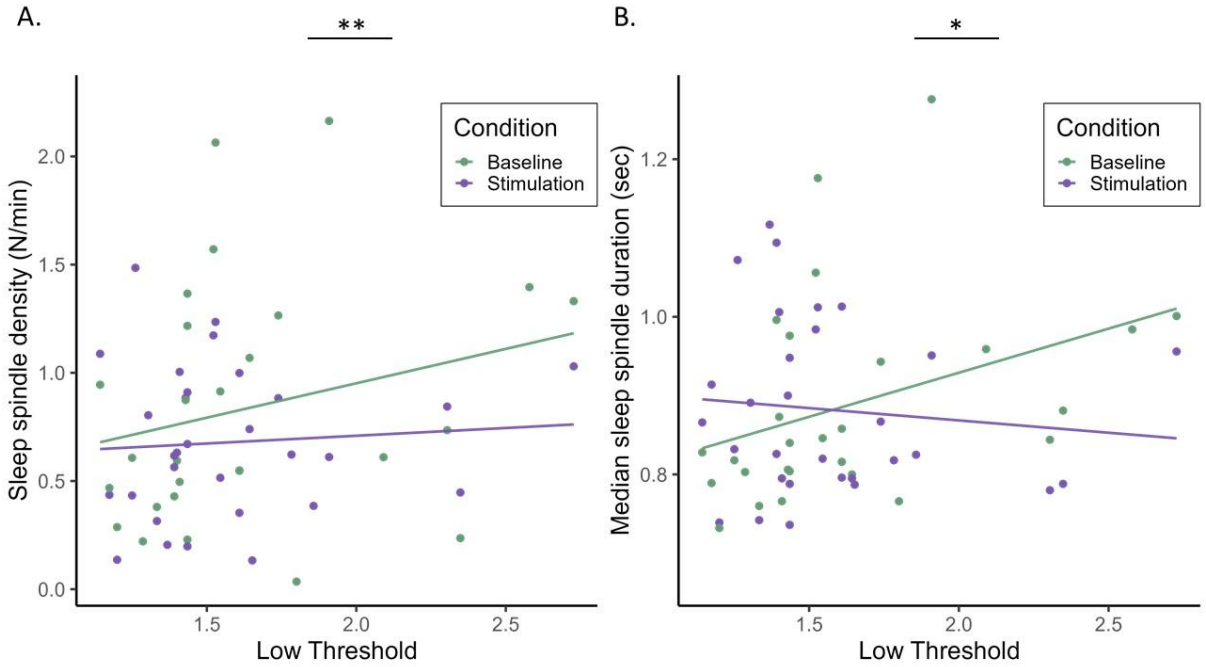

Figure 5.14 Interaction between sleep spindle features and condition. ***A.*** *Sleep spindle density and low threshold.* ***B.*** *Median sleep spindle duration and low threshold.*

5.4.2.3 Sleep disruption

Arousal density

There was no significant effect of condition on arousal density (Est. = 0.002, p = 0.837). Neither was there a significant effect of LT (-0.003, p = 0.929), nor of the interaction between LT and condition (Est. = -0.001, p = 0.973). Results remained similar after controlling for autism likelihood. Results are summarised in table 5.6.

Table 5.6 Results from the linear mixed effect model with arousal density as the outcome variable. Number of recordings = 56; Number of participants = 36. SE = Standard Error; LT = Low Threshold.

Predictors	**Estimate**	**SE**	**t**	**p**
Condition	0.002	0.011	0.208	0.837
LT	-0.003	0.029	0.090	0.929
Sex (0=M, 1=F)	0.001	0.022	0.050	0.960
Age	0.000	0.000	-0.282	0.779
Sleep position	0.023	0.002	-1.207	0.233
LT*Condition	-0.001	0.031	-0.034	0.973

Activation index

There is no difference in the AI between the baseline and stimulation nap in N2 (Est. = -0.03, p=0.407) or N3 (Est. = 0.04, p=0.259). LT is significantly and positively associated with the AI in N3 (Est. = 0.16, p=0.014, see fig. 5.15), but not in N2 (Est. = 0.117, p=0.117). A higher score on LT is therefore associated with a higher AI, meaning that individuals that are more disturbed by sensory input tend to have a more active EEG signal during N3. There was no significant interaction effect between the nap condition and LT on the AI, neither in N2 (Est. = -0.08, p = 0.339), nor in N3 (Est. = 0.08, p = 0.330). Controlling for autism likelihood status did not change the results. Results are summarised in table 5.7 for both the AI in N2 and the AI in N3.

Table 5.7 Results from the linear mixed effect models with the activation index (AI) in N2 and N3 as the outcome variables. Number of recordings = 53; Number of participants = 35. SE = Standard Error; LT = Low Threshold.

	AI N2				**AI N3**			
Predictors	**Est.**	**SE**	**t**	**p**	**Est.**	**SE**	**t**	**p**
Condition	-0.027	0.032	-0.846	0.407	0.039	0.034	1.163	0.259
LT	0.117	0.072	1.610	0.117	0.163	0.062	2.620	**0.014**
Sex (0=M, 1=F)	0.119	0.060	1.986	0.055	0.151	0.052	2.935	**0.007**
Age	0.001	0.001	1.153	0.255	0.001	0.001	0.672	0.506
LT*Condition	-0.078	0.080	-0.978	0.339	0.083	0.083	0.997	0.330

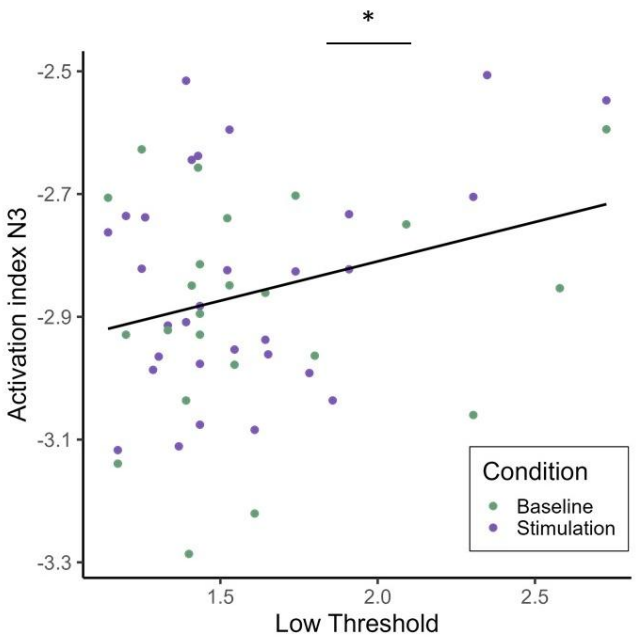

Figure 5.15 Association between Activation index in N3 and low threshold

To summarise, higher scores on LT, meaning higher sensory sensitivity, significantly associate with lower SWA and higher AI (but not the number of arousals), irrespective of the nap condition. Higher scores on LT also associate with overall lower frequency of K-complexes, throughout the Stimulation nap. There is no significant main effect of LT on any of the sleep spindle parameters. However, when there is stimulation, sleep spindle density and duration decreased significantly compared to baseline, but only in individuals with higher scores on LT.

5.5 Discussion

First, this study shows that 8-11-month-old infants process and react to auditory input during sleep, even without the presence of behavioural awakenings. Immediately after a stimulus was presented, TFR analysis showed that activity in the lower end of the frequency spectrum, in the theta and delta range, was increased in sleep stage N2. This likely results from the increased production of evoked K-complexes, which I show were increased after stimulation. Besides altered delta activity after a stimulus, TFR analysis also showed sigma activity was subsequently decreased. However, we did not find a significant decrease in individual sleep spindle occurrence corresponding with the sigma decrease.

Second, the aim of this study was to explore whether an infant's LT score, a subjective measure of an infant's behavioural and affective responsivity to sensory input, is associated with sleep protective and sleep disruptive markers and whether the presence of sensory input specifically affects infants with high scores on LT. In terms of sleep protective elements, we found that SWA in N3 and K-complexes in N2 were lower in infants with higher LT scores, irrespective of the sensory environment. When there

was auditory stimulation during a nap, sleep spindle density and duration decreased, but only in infants with higher scores on LT. For sleep disruptive markers, the AI, a measure of EEG activation, was increased in infants with higher LT scores, independent of the presence of sensory input. However, the number of micro-arousals was not.

5.5.1 Higher LT scores associate with lower spontaneous SWA and K-complexes

We find that infants with heightened sensory reactivity tend to have less slow wave occurrence and activity. One possibility is that slow wave production is altered because sensitive infants are more disturbed by sensory input during sleep. However, our findings do not support this potential mechanism, as slow waves were lower irrespective of the presence or absence of sensory input. Below we will explore what other mechanisms could explain this link between slow wave sleep and sensory profiles.

Situation of the findings in the literature

In line with these findings, Arazi et al. (2020) reported a decrease in SWA in autistic children compared to non-autistic children age 2-8-years-old. Their study revealed a difference in the first hours of the night, which disappears as sleep pressure dissipates towards the end of the night, similar to Lambert et al. (2016) that find a reduction of SW sleep in autistic children. Nguyen et al. (2022) did not find a difference in SWA in autistic and non-autistic 9-16 year-olds, however they did find more externalizing behaviours associated with lower SWA in the non-autistic children. Externalizing behaviours were extracted from the Child behaviour checklist (CBCL) and include aggressive behaviours, rule-breaking and conduct problems. Possibly, these types of behaviours share similar characteristics with behaviours evaluated in the sensory profile 2, which often draw upon behavioural and affective reactivity to the environment (e.g. Q54. ‘My child becomes so upset in a new setting that it’s hard to calm down’).

That spontaneous K-complexes are reduced in infants with higher scores on LT aligns with a study on older children (ages 6-13) that reported fewer K-complexes in autistic children than non-autistic children (Lambert et al., 2016). However, we did not replicate findings in adults, that suggest subjective noise sensitivity is related to evoked K-complexes to sound (Lechat et al., 2021). This could be because Lechat et al. focussed on noise-specific sensitivity, whereas LT captures a broader sensory profile. Additionally, the immaturity of K-complexes in infancy could have made K-complex detection less sensitive.

Our findings in infants largely seem to align with existing literature comparing SWA and K-complex occurrence in autistic and non-autistic children, as well as the association with daytime behaviours, rather than autism diagnosis. However, we provide further insight into what aspects of the autism

phenotype are associated with sleep micro-architecture by showing a particular association with a parent-reported measure of sensory processing. There are several possibilities for why SWA and LT may be associated. Either SWA drives LT, LT drives SWA, SWA and LT co-occur because both are caused by a common underlying mechanism or a combination of all three. Below, I discuss potential mechanisms that link SWs and LT.

How could this be related to sensory processing differences?

As outlined in Chapter 1 section 1.1.2, SWA partly reflects sleep pressure, with increased SWA during a recovery night after sleep deprivation and its gradual dissipation over the course of the night (Dijk et al., 1987, 1990; Esser et al., 2007; Pappenheimer et al., 1975). According to the Synaptic Homeostasis Hypothesis (SHY; See Chapter 1 section 1.1.2), SWA depends on and drives healthy synaptic functioning. Disrupted synaptic plasticity has been proposed as a potential cause of autism (Bourgeron, 2015; Guang et al., 2018), and recent research suggest that synaptic dysfunction may drive both sleep difficulties and other symptoms of autism, positioning sleep difficulties as a core symptom of autism (Doldur-Balli et al., 2022; Missig et al., 2020). Doldur-Balli et al. (2022) propose a model (See fig 5.16) where synaptic dysfunction leads to sleep difficulties and autism symptoms, but in which sleep, especially early in development, also impacts synaptic functioning (the latter is discussed below in more detail). In their model, sleep and autism symptoms also have a bidirectional relationship. The relationship between SWA and LT could be explained by this model where synaptic dysfunction drives lower SWA as well as increased reactivity to sensory input during wakefulness. While the relationship between synaptic functioning and SWs has been widely studied and modelled, how exactly synaptic dysfunction would lead to high scores on LT is less straightforward and likely complex. However, that synaptic plasticity could influence sensory processing in autism has been proposed before (Hansel, 2019). Other symptoms of autism besides sensory processing differences could also be affected by synaptic dysfunction, but one study in a similar cohort as ours show a particular link for sensory behaviours. The study finds that lower functional connectivity, a potential consequence of synaptic dysfunction, is correlated with more restrictive and repetitive behaviours (RRBs), but not social affect (O'Reilly et al., 2023). This study was run in a large sample of infants at EL and TL for autism, age 12 months. As RRBs and sensory processing differences often co-occur (Wigham et al., 2015), it is possible that underconnectivity drives lower SWA in infants with higher scores on LT. A common underlying mechanism such as synaptic dysfunction, could provide a transdiagnostic explanation of why other (neurodevelopmental) conditions have a high prevalence of sleep difficulties (Chawner et al., 2023) and potentially sensory differences.

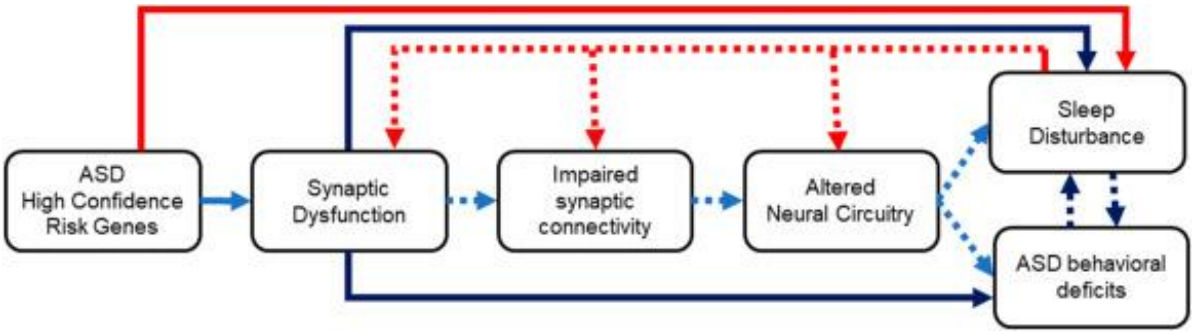

Figure 5.16 Pathway from synaptic dysfunction to sleep difficulties and autism symptoms. Figure from Doldur-Bali et al. (2022)

Besides a common underlying mechanism, it is also possible that reduced SWA drives high scores on LT. If SWA is necessary for synaptic pruning and rebalancing synaptic strength as suggested by the SHY, then it is plausible that lower SWA could impact sensory processing in both the short- and long-term.

In the short-term, one night of sleep deprivation has been shown to induce increased reactivity in the somatosensory cortex and decreased sensory gating responses the next day (Krause et al., 2019; Zhang et al., 2019). However, whether this is due to a reduction in SWS particularly is unclear, as these studies looked at total sleep deprivation rather than SW deprivation.

If SWA remains low consistently over many nights, it could have lasting effects on sensory processing in the long run. Ringli & Huber draw a link between developmental changes in SWA topography, cortical maturation, reflected by synaptic pruning, and behavioural development. For example, synaptic pruning intensifies in the prefrontal cortex during puberty, paralleled by improvements in executive functioning and a shift of the topography of SWA from central to frontal regions. Similarly, in the first year of life, maximum SWA is located occipitally, whilst at the same time synaptic density in the visual cortex decreases and visual skills are developing. If SWA would be reduced over a prolonged period, this could potentially disrupt brain and behaviour development. However, findings on SWA in early development and the effects on later behavioural outcomes are mixed. For example, a positive concurrent association between SWA and psychomotor development was found in 8-month-olds (Satomaa et al., 2020), but the frontal/occipital ratio of SWA at 6 months had no predictive power on concurrent or later gross motor and social development (Beaugrand et al., 2023). In conclusion, reduced SWA may lead to short- and long-term effects on sensory processing, however more research, e.g. using targeted SW deprivation, is needed to confirm this relationship.

Lastly, high scores on LT may drive a decrease in SWA. From the results of this study it seems unlikely that SWA is altered due to increased sensory processing during sleep in infants with high scores on LT. Also the idea that SWA would be reduced, because infants with high LT scores are more reactive to

sensory input during wakefulness seems counterintuitive. In fact, the opposite might be expected. If changes in SWA depend on awake learning experiences, then more awareness and reactivity to sensory input would result in increased SWA. Previous research has shown that the amount of sensory input received does indeed increase SWA. Sensory stimulation of one hand before sleep results in an increase of SWA in the opposite hemisphere in the somatosensory area while immobilization led to a decrease in SWA (Kattler et al., 1994; Vyazovskiy et al., 2000). Although in this study we did not investigate topographical effects, an increase in global SWA rather than decrease would be expected in highly reactive infants if high scores on LT were driving SWA.

In summary, our findings suggest that SWA and LT scores are associated, but likely not because SW production during sleep is altered by sensory input in more sensitive infants. It may be that a common underlying mechanism drives both, such as synaptic dysfunction. Alternatively, altered SW production may increase long- and short-term sensory atypicalities, and potentially other features of autism, such as language learning difficulties (Fletcher et al., 2020). A potential link with learning will be discussed in more detail in Chapter 6.

5.5.2 Arousibility

While neither the number of arousals nor activation index increased in the stimulation nap compared to the baseline nap, the activation index did associate with LT scores, such that higher LT scores predicted higher activation indices in N3. This indicates that infants with high LT scores had higher cortical 'activation', regardless of presence or absence of sensory input. It is possible that individuals with sensory atypicalities have higher levels of subthreshold arousal activity, that not necessarily results in detectable arousals. However, these higher levels of cortical activation could still affect subjective rating of sleep, as demonstrated by Lecci et al. (2020). Alternatively, the association between AI and LT is driven by the lower SWA in infants with high LT scores, as the AI is calculated as the ratio of beta activity over SWA. While AI and SWA are correlated ($r = -0.45^{***}$ in N3 and $r = -0.33^{***}$ in N2), this is only a medium effect size association, suggesting that they may still independently be predicted by LT.

5.5.3 Do sleep spindles decrease in the face of noise?

The results of the sigma and sleep spindles analyses are less coherent compared to those for SWA and K-complexes. We observed a significant decrease of activity in the sigma range after stimulation, which we expected to coincide with a decrease is sleep spindle likelihood. However, automated detection of sleep spindles did not show a significant decrease in sleep spindle likelihood in the stimulus OFF compared to stimulus ON window. The reduction of sigma power after stimulation, but not the number of sleep spindles, may be because stimulation disrupts ongoing sleep spindles, but does not reduce

their occurrence. Sela et al. (2016) found that stimulation, both salient and non-salient, tends to terminate ongoing sleep spindles prematurely. Similarly in humans, Rudzik et al. (2018) found that transportation noise does not effect spindle density, but rather that duration and amplitude of the spindles decrease when comparing a noisy vs silent night sleep. In young infants, sigma activity also decreases during startles and sighs (Wulbrand et al., 1998). The authors suggest that a decrease in spindle activity could serve as a marker for brainstem arousal. This could explain why we do not observe a significant difference in the number of sleep spindles before and after stimulation here, but rather see a decrease in power, perhaps due to the shorter duration of sleep spindles in the stimulus ON period.

In the context of the sleep spindle gating theory, our findings suggest that stimulation disrupts sleep spindles, or at least sigma activity, rather than actively upregulating sleep spindle production. These findings are not in agreement with studies that find that sleep spindles are actively upregulated in response to sensory input (Ameen et al., 2022; Sato et al., 2007). While it remains possible that spindles protect sleep by interrupting sensory input, we did not specifically investigate the effects of the timing of stimulus presentation (during or sleep spindle evens or not) on further sensory processing or arousal probability in this study.

Despite the observed decrease in sigma activity after stimulation, there was no significant effect of stimulation on overall sigma activity during the entire N2 period, as sigma activity was not significantly lower in N2 of the stimulation nap compared to the baseline nap. This suggests that the decrease in sigma activity was short and transient, without a lasting impact on further sleep spindle production.

When comparing the baseline to stimulation nap, we found that sleep spindle density and duration decrease in the stimulation nap, but only in infants with high scores on LT. Surprisingly, when inspecting the results visually, infants with high LT scores tend to have higher sleep spindle density and duration during the baseline nap, which then decreases in the stimulation nap, though not falling below other infants with lower LT scores. It is important to note that there is no significant positive association between LT and sleep spindle density or duration, however, p-values are close to significant in both cases (sleep spindle density: $p=0.100$, sleep spindle duration: $p = 0.087$). One possibility is that for those infants that have more and longer sleep spindles the chance that the stimulation coincides with a sleep spindle, and possibly disrupting it, is higher. To confirm this, a follow-up study should be conducted with more frequent stimulation that targets sleep spindles.

For the time-locked analyses we did not look at other sleep spindle characteristics, such as duration, because of the low numbers of detected sleep spindles in such short time windows. Thirteen of the 31 stimulation recordings did not have a single detected sleep spindle in either the ON of OFF window.

This left us with only 18 recordings, some of which had low numbers of sleep spindles, which jeopardizes the reliability of the estimates of average sleep spindle characteristics.

Sleep spindle duration and low threshold

A handful of studies looked at differences in sleep spindle duration between autistic and non-autistic individuals and found either no difference (Fletcher et al., 2020; Mylonas et al., 2022) or shorter sleep spindles in autistic individuals (Farmer et al., 2018). In contrast, in this study we found a marginal association of longer sleep spindle duration, rather than shorter, with high LT scores. However, it is important to consider that sleep spindle duration changes dynamically with age and might therefore reflect different functions or processes at different ages. The aforementioned studies focussed on children older than 2 years, which may explain the different findings. In the age range of this study, sleep spindles duration may be more variable depending on an infant's developmental trajectory. As described in Chapter 4, early sleep spindles tend to be longer, likely reflecting an immature thalamo-cortical circuit. In particular, inhibitory cortical input to thalamocortical networks is essential for the termination – and as a consequence the duration - of sleep spindles (Bartho et al., 2014). Changes in sleep spindle characteristics, such as the long duration, have been suggested to reflect the shift in GABA-ergic functioning from excitatory to inhibitory that happens in the first year of life (Chegodaev et al., 2022; Peerboom & Wierenga, 2021). Animal studies show that alterations in the timing of the postnatal GABA shift, have effects on behavioural outcomes later in life, both accelerated and delayed GABA shifts. Delayed GABA shifts result in reduced social behaviour, increased anxiety, impaired sensory sensitivity and long-term memory (Peerboom & Wierenga, 2021). Thus, sleep spindle duration in the first year of life could be a marker of the GABA shift, with longer sleep spindles potentially reflecting a delayed GABA shift. Within person studies are needed that map the development of sleep spindle characteristics over the first year of life in detail. Those developmental trajectories might accurately predict behavioural outcomes later in life. Although in this study sleep spindle duration was only marginally associated with LT and in the opposite direction than expected based on the studies in autistic children, it does highlight that spindle duration would be an interesting feature to investigate particularly in the first year of life.

5.5.3.1 Methodological limitations

For the interpretation of the sleep spindle results, it is important to address the limitations of the automatic sleep spindle detection, which as described in detail in Chapter 4, under-detects sleep spindles compared to human visual detection. That sigma decreases after a stimulus, but not sleep spindle occurrence, may just be a reflection of the imperfect sleep spindle detection. Additionally, the interaction effect of nap condition and LT on sleep spindle density and duration, could be because longer sleep spindles are detected more easily, while shorter sleep spindles may not be picked up by

the detection algorithm. We would perhaps be more confident in these results if the same interaction effect appeared for sigma activity in N2, but that effect, although in the same direction, was far from significant (p=0.436).

Nevertheless, these results highlight the importance of sleep spindle duration as a measure for future work in infancy for three reasons. From a methodological standpoint, sleep spindle duration may be a more robust measure than sleep spindle density. Sleep spindle density is more reliant on the performance of the automated detection algorithm, while sleep spindle duration, even if underestimated by the algorithm, is likely affected to the same extent across all the detected sleep spindles. From a developmental standpoint, if one is interested in a marker for brain maturation for example, sleep spindle duration may be the most reliable of the commonly used sleep spindle features, as it is least affected by homeostatic processes (Knoblauch et al., 2003). Sleep spindle density for example is well known to decrease after a night of sleep deprivation in adults (Fernandez & Lüthi, 2020). Sleep spindle duration could therefore be a more reliable individual marker, less reliant on previous sleep. Thirdly, in relation to sensory processing during sleep, this measure in particular is affected by sensory input in rats (Sela et al., 2016), adults and elderly (Rudzik et al., 2018). Also for memory researchers, sleep spindle duration might be of particular interest, as it was found to predict the stabilization of new semantic knowledge, whilst sleep spindle density was not (Fletcher et al., 2020).

Furthermore, these discrepancies between measures highlights the need to include multiple measures for sleep spindle activity in future work. A good practice could be to include more robust measures such as sigma activity besides measures that are highly dependent on algorithm performance, like sleep spindle occurrence or density. This is of particular importance for studies in populations which have atypical sleep spindle features. These analyses show that sleep spindle density and sigma activity, which are often used interchangeably in the literature, can give rise to different results, and therefore different conclusions.

5.5.4 Does the type of stimulation matter?

In this study, pairs of pure tones were played during a nap. While there were clear markers of the stimuli being processed (ERPs and TRF analyses), stimulation seemed to have a minimal effect on sleep macro-architecture, arousibility or sleep micro-architecture. In adults, the more salient a stimulus is, such as emotional tones or unfamiliar voices, the larger the neural response to that stimulation (Ameen et al., 2022; Blume et al., 2017). It is possible that more salient stimulation will have a larger effect on infant sleep. Blume et al. (2021) investigated the effect of traffic noise on infant sleep across the first year of life, using actigraphy at home. Interestingly, they found a decrease in the duration of

night-time sleep, but only in infants that did not have an older sibling, which they attribute to an adaptation to habitual noise from the sibling. They did not find any effects of traffic noise on night awakenings or night-to-night variability in sleep. Similarly, we only found an effect of auditory stimulation on nap duration, but not other macro-architecture variables or arousibility. In contrast to Blume's study, infants in this study had an older sibling. However, infants slept in a new environment with an EEG cap, compared to in the comfort of their own home wearing only a watch in Blume's study. It is well known that sleepers are more vigilant when they sleep in a new environment (first night effect), although this is not as pronounced during infancy (Rebuffat et al., 1994). It is therefore possible that in this study, infants, although accustomed to a noisy sibling, were in an increased state of vigilance in the lab environment which affected their nap duration.

5.6 Implications and conclusion

This study is the first to demonstrate that subjective caregiver reports of an infant's sensory profile are associated with objective measures of sleep depth. This finding is important as it confirms that the relationship often observed in the literature between subjective reports of sleep and sensory sensitivity is not solely influenced by the caregiver's profile, as discussed in Chapter 3. Additionally, the study validates the reliability of caregivers' assessments of their child's sensory profiles, providing empirical support for their use in both clinical and research settings. Furthermore, it highlights the potential for using subjective reports to identify infants at risk for sleep difficulties, and could be used for early detection and intervention.

Our findings have implications for sleep practices in infants with and without sensory atypicalities. Sensory input, at least simple, non-salient auditory input, is registered by 8-11 month old infants, even without causing a behavioural awakening. While auditory stimulation does not significantly impact nap macro- or micro-architecture, it does shorten an infant nap. Future studies should explore whether salient input has larger effects on a nap. Furthermore, a question that still remains is whether a slightly shorter nap has significant impacts on daytime functioning.

Our findings open new avenues of research for testing the causal links between SWA and sensory processing. Recently, new non-invasive methods have been developed to increase SWA through closed loop auditory stimulation (Ngo et al., 2013). With this method, SWs are detected online during sleep and are 'hijacked' by introducing an auditory stimulus in the upstate of the slow wave. This introduces a train of slow waves. Targeting the improvement of slow waves could potentially benefit infants with sensory sensitivities. Other behavioural methods exist as well to improve slow wave activity, for example working memory training increases SWA in children (Pugin et al.,2015). However, it is unknown whether these would be effective in individuals with sensory atypicalities.

Chapter 6.
Discussion

Accumulating evidence shows that sensory processing differences often associate with sleep difficulties (Appleyard et al., 2020; Engel-Yeger & Shochat, 2012; Hartman et al., 2022; Mazurek & Petroski, 2015; Tzischinsky et al., 2018b). This may not be surprising, as one of sleep's defining features is that the sleeper is partly unresponsive to sensory input from the environment. Sleep onset and maintenance are facilitated by reduced processing of environmental stimuli and an overall reduction of brain activity. The former is either achieved by simply avoiding strong external stimulation or by effective filtering of irrelevant or redundant sensory information, or a combination of both (Coenen, 2024). Atypical gating of sensory simulation is common in autism and emerges early in development. Infants at elevated likelihood for autism as young as eight months show increased neural responsivity to repeated auditory stimulation (Kolesnik et al., 2019) as well as decreased gating of tactile input (Piccardi et al., 2021). If an individual does not effectively gate incoming sensory input either in the run-up to sleep or during sleep, their sleep may be affected. Alternatively, both sensory processing and sleep difficulties may stem from a common underlying mechanism, such as altered synaptic function or an excitation/inhibition imbalance. Lastly, poor sleep may induce or exacerbate sensory responses. The relationship between sleep and sensory processing is likely complex, with multiple pathways—such as those described above—interacting simultaneously.

The main aim of this thesis is was to better understand whether sensory processing differences drive sleep difficulties, due to poor gating of sensory input. Determining cause and effect is important for the development of intervention strategies. Because early sleep is critical for healthy brain development, we focussed on sleep and sensory processing in the first year of life. The improvement of sleep in infancy may have immediate benefits for health and wellbeing of the infant and caregiver (Eyuboglu & Eyuboglu, 2020), and could also have long lasting effects on behavioural outcomes later in life (Cook et al., 2020; Jaramillo et al., 2023; Mäkelä et al., 2021) .

Studies investigating sensory processing and sleep often focus on autistic individuals, because sleep and sensory differences are highly prevalent in autism (Lane et al., 2022). However, the relationship between the two variables seems to extend beyond autism diagnosis as the same association is found in non-autistic individuals (Hartman et al., 2022; Vasak et al., 2015). Therefore, in this thesis, I investigate the pathway between sensory processing and sleep in infants at typical and elevated likelihood for autism, a population with a broad range of sensory processing differences.

In this last chapter, I will summarise the key empirical findings, discuss theoretical implications, considerations for the study of sleep and sensory processing in infancy and potential avenues for further research.

6.1 Summary of findings

6.1.1 Sensory processing measures predict sleep onset and night awakenings

Across Chapter 2 and 3, I looked at the effects of two sensory processing measures on sleep onset latency and night awakenings. The sleep measures were assessed by caregiver report and reflected the average sleep onset latencies and night awakenings in the past week.

Using a longitudinal secondary dataset, we had measurements of 134 infants at EL and TL for autism at 5, 10 and 14 months. In Chapter 2, I first asked whether trajectories of sleep onset latency and night awakenings differed between infants at EL and TL for autism. Indeed, while sleep in infants at TL tended to improve – less night awakenings and shorter sleep onset latencies – over the course of the study, infants at EL did not show the same improvement. From 10 months onwards, infants at TL had significantly less night awakenings and shorter sleep onset latency than infants at EL. This was the first study to show sleep differences in infants at EL compared to infants at TL longitudinally in the first year of life.

I then investigated whether these differences in sleep could be explained by differences in sensory gating, measured as repetition suppression in response to pairs of tactile stimuli when the infant was awake. I found that at 10 months of age, the extent to which an infant gated sensory input during wakefulness predicted how long it took them to fall asleep. This may indicate that the suppression of irrelevant information is necessary to fall asleep quickly. However, poor sensory gating did not predict the frequency of night awakenings. This indicates that gating mechanisms during wakefulness and sleep differ, in line with previous studies in adults (Kisley et al., 2001).

Next, I investigated whether sensory profiles, and in particular low threshold – the combined subscales sensory sensitivity and sensation avoidance – predicted sleep independently of sensory gating. We initially expected a correlation between low threshold scores and sensory gating, so that infants that gate sensory input less well on a neural level would also be hyperreactive on a behavioural and affective level. However, tactile gating and low threshold scores were not correlated. Furthermore, when we controlled for an infant's low threshold score, both low threshold and sensory gating predicted sleep onset latency independently of each other. Whilst sensory gating did not predict night awakenings, low threshold did. Infants that are more sensitive and avoidant of sensory input generally have more night awakenings. Parental reports of sensory profiles therefore more broadly explained sleep differences, while a neural measure of sensory gating showed a specific association with sleep onset.

In all these models, sensory processing differences predicted sleep irrespective of on infant's autism likelihood status. This suggests that a general mechanism links sleep and sensory processing as

confirmed by studies showing the same association in non-autistic individuals (Appleyard et al., 2020; Hartman et al., 2022; Kılıç et al., 2024).

One key assumption of causality is that the cause precedes the effect in time. Therefore, in Chapter 3 I tested whether early sensory differences predict later sleep difficulties and/or vice versa, taking advantage of the longitudinal design of the dataset. A RI-CLPM was used to appropriately account for the stability of the measures over time within the same person, e.g. some infants will have more night awakenings than others at all time points, but still show a decrease from one visit to another compared to their younger selves. Indeed, we found that both sensory profiles and night awakenings are highly stable over time. Individuals that tend to wake up frequently at night – in comparison to others – will likely do so at 5, 10 and 14 months. The same was true for sensory profiles, high scores on LT were highly stable over time. Moreover, these stable traits were correlated. Infants that generally woke up frequently, also generally had high scores on low threshold. When investigating the within-person effects, there were no significant concurrent state-like correlations at each timepoint. A deviation in sleep from the usual did not relate to a deviation in sensory profiles from the usual. The within-person cross-lagged effects were also not significant. A deviation in low threshold at an early timepoint did not predict a later deviation in sleep. Therefore, there was no evidence that early sensory processing differences drove later night awakenings. However, these results need to be interpreted carefully. We may not have found any evidence for a temporal precedence of sensory differences, but this could be due to the timeframe and timescale used in this study. Due to the spread of the measurements – several months apart – we can only conclude that between 5 and 14 months of age sensory processing differences do not drive night awakenings several months later. It is still possible that sensory processing differences drive sleep difficulties on a smaller time scale, e.g. the following night or week. None of the models with sleep onset latency could be interpreted due to improper solutions or poor model fit.

6.1.2 Sleeping sensory profiles in a noisy environment

If sensory differences drive sleep problems, we would expect that sensory input during sleep would affect sleep differently in those with heightened sensory profiles. To test this hypothesis, I focused on the effects of sensory input on markers during sleep associated with sleep protection – SWs (including K-complexes) and sleep spindles – and sleep disruption – arousals and EEG activation.

However before doing so, I ensured that methods to detect sleep spindles and K-complexes were adapted to the age range used in the SNOOSE study (8 to 11 month-olds), which is described in Chapter 4. In infancy, sleep spindles tend to have a lower amplitude and the background EEG signal is often higher, which results in an under-detection of sleep spindles compared to manual sleep spindle

detection. I improved the performance of an existing automatic detector from the YASA package by adjusting the threshold settings systematically. This resulted in a significant improvement, with an F1-score of 0.55 for the adapted algorithm compared to 0.4 with the default setting. An F1-score of 0.55 is acceptable – but not optimal – and similar to other algorithms used in the field (Kwon et al., 2023). Additionally, the correlation between the algorithm's detected sleep spindle density and the manually detected sleep spindle density was significantly higher for the adapted algorithm. This gave us confidence to proceed with the improved algorithm.

K-complexes are still immature in infancy and difficult to discern from background activity and from other SWs. Therefore, in Chapter 4, I explored whether *evoked* K-complexes could be identified by taking advantage of the reliable timing of a K-complex in response to a stimulus. However, it was unclear from the literature whether the timings of evoked K-complexes are similar in infancy and adulthood. In adults the negative peak of an evoked K-complex tends to occur within 450 to 700 ms after stimulus onset. Results from the SNOOSE cohort revealed a clear increase in SWs after stimulation in a similar time-window as adults. We therefore concluded that these are likely evoked K-complexes and continued in the following analyses with this method.

In Chapter 5, I first showed that the sensory input, 60 Db pure tones in pairs, were registered during sleep even without any behavioural awakenings. Using Time Frequency Representations, I demonstrated that activity in the sigma range decreased and activity in the delta range increased after a stimulus in sleep stage N2. The latter likely due to an increase in evoked K-complexes after stimulation, which were indeed significantly more abundant after a stimulus compared to before. The decrease in the sigma activity was expected to correspond to a general disruption of sleep spindle production due to stimulation. However, there was no significant decrease of sleep spindles after stimulation compared to before. On a larger timescale, we also observed that nap duration was shorter (approximately 10 min on average) when there was stimulation, but infants did not have more arousals or altered sleep architecture due to stimulation.

Next, the effects of sensory profiles and their interaction with external sensory input on sleep protective and disruptive markers was investigated. We found that infants with high scores on LT had significantly lower slow wave activity in N3 as well as less K-complexes in N2, irrespective of the presence of sensory input. Sleep spindle density and duration decreased in the stimulation nap compared to the baseline nap, but only in infants with higher scores on LT. Arousal density was not increased in infants that score high on LT, nor was it increased when there was stimulation. However, the activation index (AI), a measure of EEG activation (ratio of beta/delta), was increased in infants with higher LT scores, irrespective of the nap condition.

In conclusion, in terms of sleep protective markers, infants that score higher on LT have lower SWA independent of the sensory environment around them. Sleep spindle density was decreased in the stimulation nap, but only in infants with higher scores on LT. In terms of sleep disruptive markers, LT scores did not affect arousal density, but did affect the AI, with more EEG activation in infant with higher scores on LT, independent of the presence of sensory input during a nap.

6.2 Theoretical implications

In the next part, I discuss the wider implications of some of our findings. I explore why SWA may be reduced in highly sensitive infants and how that could relate to memory consolidation. I then focus on the importance of sensory processing when falling asleep and during sleep in infancy. Furthermore, I discuss the importance of choosing the right measurements and methods demonstrated by the studies in this thesis. Throughout, I highlight pathways that future research could explore. But first, I address to what extent our findings provide support for a causal pathway from sensory processing differences to sleep difficulties.

6.2.1 Do sensory processing differences lead to sleep difficulties?

In Chapter 1, I identified three pathways that could explain the co-occurrence of sensory differences and sleep difficulties (See figure 1.11): 1. Sensory processing difference may cause sleep problems; 2. sleep problems may cause sensory processing differences; or 3. they may arise independently, and an underlying mechanism may cause sleep problems and sensory differences. In this thesis, we aimed to tease apart these three pathways. I hypothesized that sensory processing differences lead to sleep problems (pathway 1), due to the ineffective gating of sensory input during sleep. Three research designs were used to address this question: a cross-sectional, a longitudinal and an experimental design. For a causal relationship to be established, the consensus is that three criteria need to be met: a correlation between cause and effect, temporal precedence of the cause, and a lack of plausible alternative explanations.

In support of the first criteria, Chapter 2 demonstrates that both tactile gating and sensory profiles predict sleep onset and night awakenings – a first indication that sensory processing differences may lead to sleep problems. Then we set out to test whether sensory processing differences preceded sleep difficulties in Chapter 3. Initially, partial correlations indicated that early sensory profiles predicted later sleep, but not vice versa. However, after accounting for between-person variance in sleep and sensory profiles, changes in an individual's sensory profile no longer predicted subsequent changes in night awakenings. Instead, we observed a strong correlation of the between-person latent variables of sensory profiles and night awakenings. This suggests that both may be driven by a shared underlying

mechanism, that temporal precedence might occur earlier than captured in our study, or that these effects manifest over shorter timescales, such as day-to-day variations, rather than over months.

In the last study, we shifted our focus from changes in sensory profiles to how different sensory profiles interact with the sensory environment during sleep. We again investigated effects on the within-person level. We asked whether sensory input differentially impacted sleep depending on an infant's sensory profile, expecting that infants that are more sensitive would show greater sleep disruption or weaker sleep protective responses to sensory input. We found tentative evidence supporting this hypothesis regarding sleep spindles: Sensory input led to a reduction in sleep spindle density and duration, but only in hypersensitive infants. These findings suggest that sensory input may disturb sleep spindle production in infants that score high on LT, which could be a potential mechanism that drives sleep difficulties in these infants. Disrupted sleep spindle production may increase vulnerability to external disturbance during sleep and could additionally have knock-on effects on memory consolidation (Peyrache & Seibt, 2020). However, we did not observe an interaction effect of sensory profiles and arousibility, and therefore it is still unclear what the effects are of the decreased sleep spindle density and duration in infants with high scores on LT. Furthermore, the lack of a similar result when using sigma activity as a measure of sleep spindle activity raises questions about whether these results may be driven by suboptimal sleep spindle detection. To confirm these findings, the results should be replicated in a different cohort.

For two sleep measures we found an association with sensory profiles that was independent of the sensory environment. The amount and power of SWs associated with an infant's sensory profile: The more sensitive an infant is the less deep their sleep, whether or not there was sensory input. Similarly, more sensitive infants also had more 'active' brain activity, as measured by the activation index (beta/delta activity), but again independent of the sensory environment. These findings suggest an association with sleep, that does not seem to be driven by ineffective gating of sensory input during sleep.

Whilst these studies do not rule out the possibility that sensory processing difficulties lead to sleep difficulties, they offer more support for a common underlying mechanism driving both symptoms. Throughout this thesis, several potential common factors have been identified that may contribute to sleep difficulties and sensory processing differences and that are related to autism. The focus on specific sleep and sensory characteristics in these studies may help pinpoint potential underlying factors that affect both symptoms. In Chapter 2, we observed that gating during wakefulness only associates with sleep onset but not night awakenings. As discussed in detail in there, this may indicate altered GABAergic functioning. Lower GABA levels or mutations in GABA-receptors are associated with

longer sleep onset latencies (Agosto et al., 2008; S. Kim et al., 2019), altered sensory processing differences, such as lower detection thresholds for somatosensory input (Puts et al., 2017) and are common in autism (Coghlan et al., 2012). In Chapter 5, we find a strong effect of LT scores on SWs, which may indicate atypical synaptic functioning as an underlying mechanism, which is also thought to be altered in autistic individuals (Doldur-Balli et al., 2022). Interestingly, SWs are not only thought to depend on, but also to drive healthy synaptic functioning (Cirelli, 2013), which may suggest a pathway from altered SWA to synaptic dysfunction, which in turn could lead to sensory processing differences, in support of pathway 2. Below, I discuss in more detail how this may be related learning and memory.

In conclusion, the findings in this thesis confirm that there is a clear association between sensory processing measures and sleep measures already early in development. A particular role for SWs was uncovered in relation to sensory profiles. Sensory gating during wakefulness relates to sleep onset latency, but not night awakenings. We do not find clear evidence of a causal relationship from sensory processing differences to sleep difficulties. Instead, our findings lean slightly more towards an underlying mechanism driving both sleep and sensory differences. Additionally, our findings highlight the need for research that tracks within-person changes in sensory processing measures and the effects on sleep the same day.

6.2.2 Lower slow wave activity: Underlying mechanisms and implications for learning

The results of Chapter 5 show that reduced SWA is associated with higher scores on LT. However, it remains unclear whether reduced SWA indicates a reduced need for sleep or whether it reflects an inability to effectively build up sleep pressure despite the need for it. Additionally, it is unclear whether having lower SWA compared to peers has negative consequences. Let us explore these two questions.

In regards to the homeostatic properties of SWA, a study in one particular mouse model of autism (*Shank3*$^{\Delta C}$) – with a truncation in the *Shank3* gene, which encodes a neural junction protein critical for synaptic function– looked at the dynamic effects of sleep loss on sleep the next day (Medina et al., 2022). Firstly, *Shank3*$^{\Delta C}$ mice exhibited disrupted sleep onset adaptations to sleep deprivation. Whereas wild-type (WT) mice fell asleep quicker after sleep loss, the *Shank3*$^{\Delta C}$ mice had long sleep onset latencies despite previous sleep loss. Regarding SWA, the study shows that SWA is decreased at baseline in *Shank3*$^{\Delta C}$ mice, similar to findings in humans (Arazi et al., 2020). Nevertheless, *Shank3*$^{\Delta C}$ mice did show increased SWA after sleep deprivation, indicative of intact SWA dynamics in response to sleep loss. This suggest that homeostatic responses to sleep are intact in autistic individuals in terms of SWA. Indeed, in autistic children, SWA decreases over the course of the night – another typical homeostatic feature of SWA - despite being lower than in non-autistic children in the first hours of the

night (Arazi et al., 2020). These studies demonstrate that lower SWA does not necessarily indicate that homeostatic regulation of SWA is absent, as both a build-up of SWA is seen in mice after sleep deprivation and a dissipation of SWA over the course of the night in humans. However, it may be that the build-up of sleep pressure is weaker.

However, the question remains: why is SWA lower at baseline in infants that have higher scores on LT or in autistic children? According to the synaptic homeostasis hypothesis (SHY; see Chapter 1 section 1.1.2), synaptic strength increases during the day, which results in larger SWA. During the night, synaptic strength renormalized and SWA dissipates, facilitating new learning the next day. Arazi et al. (2020) did not find significant differences between autistic and non-autistic individuals in SWA and SW slope in the second half of the night, suggesting that synaptic renormalization reaches normal levels in both groups by the morning, according to SHY. Lower SWA at the beginning of the night on the other hand may suggest that the overall increase of synaptic strength during the day is lower or less rapid than non-autistic peers. This could reflect either altered synaptic function, as discussed in Chapter 5 section 5.5.1, and/or potential learning differences, as according to SHY, it is not just neuronal firing that causes an overall increase in synaptic strength but learning specifically.

Indeed learning difficulties are common in autism (Boucher & Anns, 2018; Kercood et al., 2014). That sensory gating is altered in infants at EL for autism, as shown in Chapter 2, could also indicate a learning impairment, as habituation may be seen as the simplest form of learning (McDiarmid et al., 2019). The ineffective build-up of SWA could indicate difficulties with encoding of information during the day. It is possible that sensory hyperreactivity interferes with the effective encoding of information. Keith et al. (2019) find that autistic adolescents perform similarly to non-autistic peers on a working memory task, however once broadband noise was added in the more difficult version of the task, performance was worse in the autistic group and autonomic arousal levels measured by heart rate increase. Individuals that feel overwhelmed by sensory input may show particularly ineffective learning, which may result in decreased upscaling of synapses, which may in turn lead to lower SWA at night. Further research could investigate this pathway.

Reduced SWA may in turn have implications for memory consolidation. SWA has consistently been linked to better performance on declarative memory tasks in healthy adults (Rasch & Born, 2013), with studies showing an association between higher SWA and better task performance (Holz et al., 2012; Simon et al., 2017), and that boosting SWA can enhance memory performance (Crupi et al., 2009; Harrington & Cairney, 2021). Additionally, local increases of SWA over brain regions involved in the pre-sleep learning task demonstrate a convincing role of SWA in memory consolidation. However, when looking at atypical populations, the magnitude of overnight improvement on task performance

is not always related to SWA, e.g. in dyslexic children (Smith et al., 2018) and children with ADHD (Prehn-Kristensen et al., 2011). Similarly, a study in autistic children did not find a relationship between SWA and next day task performance. However, it should be noted that in this particular study the control group also did not exhibit the relationship (Maski et al., 2015). In this study and others, overnight task improvement did occur in the autistic group, despite no relationship with SWA (Knowland et al., 2019). It has been suggested that autistic individuals may use compensatory strategies, such as increased hippocampal recruitment during encoding (Hogeveen et al., 2020). Therefore, it is unclear whether lower SWA may negatively affect learning. Further research could investigate the role of SWs and memory consolidation in relation to sensory profiles, rather than autism diagnosis.

6.2.3 Improving measurements and the search for the 'right' methodology

A theme which emerges throughout this thesis is the importance of selecting the right methodology and measurements. Below I discuss how the results in Chapter 3 showed the importance of the separation of within- and between person effects to understand causation. Then I discuss visual detection of sleep spindles and recent advances in the field that go beyond the current gold standard.

Within- and between-person effects

In Chapter 3, I demonstrated that the separation of within- and between-person effects can significantly change the interpretation of results. Initially, partial correlations suggested a one-directional relationship: early sensory processing predicted later sleep, but not the opposite way around. This might have led us to incorrectly assume the effect was driven by within-person variation and inferred that changing an individual's sensory profile could alleviate long-term sleep difficulties. However, when we separated within- and between-person effects using a RI-CLPM, it seems that the results from the partial correlations were primarily driven by between-person differences. An effect on the between-person level is not less valuable or interesting than an effect in the within-person level, but the interpretation of the results is different. These between-person findings inform us about a predictive relationship: infants with heightened sensory profiles likely also experience sleep difficulties or are at risk of developing sleep difficulties in the future. A similar longitudinal study with two timepoints in autistic children, found that sleep and sensory symptoms covary over time (Manelis-Baram et al., 2021). They conclude that an intervention in one of the variables will likely improve the other variable. Had they been able to separate within- from between-person effects, they may not have come to the same conclusion. It should be noted that they also acknowledged that a common underlying mechanism may drive both. Our study shows that improving sensory symptoms between 5 and 10 months of age may not significantly improve the trajectory of night awakenings months later, contrary to what we might have concluded without differentiating within- and between-person effects.

Nonetheless, the between-person effects indicate that infants who experience sensory differences at 5 months may already benefit from an intervention targeting sleep, although not necessarily by improving sensory symptoms.

This showcases the importance of using the right statistical methods for the research question. When asking about causal within-person effects, appropriate statistical methods should be used that are able to distinguish within- from between-person effects.

The future of sleep spindle measurements

In Chapter 4, we showed that automated detection algorithms trained on adult data do not perform as well in an infant dataset, a problem also recognised by others (Berja et al., 2024; L. Wei et al., 2022). These studies, like ours, aimed to improve the algorithm performance in comparison to manually annotated sleep spindles, a necessary step to increase the reliability of sleep spindle counts in infancy and build normative data on sleep spindle development. However, this assumes that manual detection represents the 'ground truth'. In essence, we improved the agreement between the algorithm and human, but does the human detection truly capture the underlying biological reality?

Sleep spindles are visually detected in the time representation of the EEG signal, but all frequencies are mixed into one signal. As described in Chapter 4, the visibility of sleep spindles therefore depends on the activity in other frequency bands that happens at the same time. For example, sleep spindles are harder to identify when they occur simultaneously with a slow wave. High background activity is a particular issue in infant sleep recordings. This raises the question of whether sleep spindles that are not as visible to the human eye in the EEG signal are not real and functional sleep spindles? A question which has been asked by others in the field.

Recently, Dimitrov et al. (2021) investigated an alternative method of sleep spindle detection based on time-frequency representation of the signal rather than just time representations (see figure 6.1). They find clear demarcated increases in sigma activity, which they call TFσ peaks, that often overlap with visually detected sleep spindles in the time signal, but also reveal many more peaks that are not as visible (or would not be identified as a sleep spindle) in the time representations. They suggest that classically defined sleep spindles are only a subset of a larger class of events. The detected TFσ peaks are a broader phenomenon from the same underlying event. Dimitrov et al. highlight that the classic definition of a sleep spindle is based on an arbitrary cut-off – what is visible to us in the EEG signal.

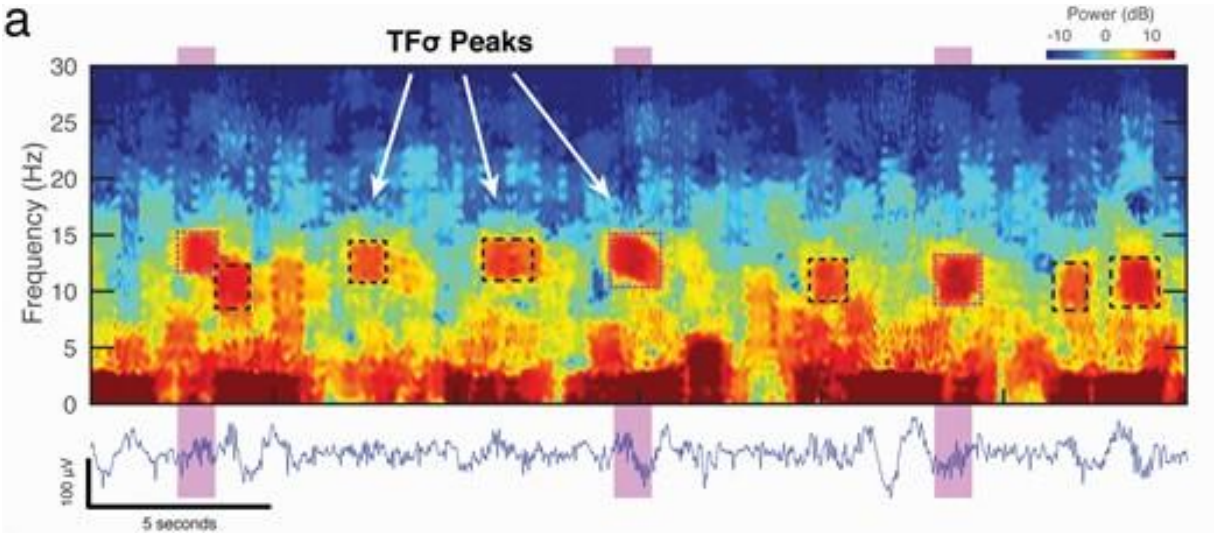

Figure 6.1 Time-frequency sigma peaks. Purple squares represent TFσ peaks that overlap with visually detected sleep spindles in the time signal. Black squares are TFσ peaks that do not overlap with a classic sleep spindle. Figure adapted from Dimitrov et al. (2021).

This raises the question whether the visibility of a sleep spindle on scalp EEG recordings matters for its functionality? In other words, does a sleep spindle that stands out less do just as good of a job as a very visible sleep spindle? A recent study in mice investigated whether the 'quality' of a sleep spindle is related to its functionality (Blanco-Duque et al., 2024). The study parameterized the strength of oscillatory events in the sigma range using 'damping', a metric that captures the decay in the amplitude of and oscillation and therefore reflects the strength and stability. The authors named this measure o-Quality. The study found that the o-Quality of a sleep spindle is related to its distribution and spatiotemporal dynamics and reflects the degree of network synchronization, e.g. local sleep spindles have a lower o-quality than global ones. In terms of functionality, higher o-Quality sleep spindles are more often coupled with slow waves and provide greater sleep protection. The latter was demonstrated by an inverse relationship with behavioural responsiveness – measured with muscle twitches – to auditory stimulation.

The study by Dimitrov et al. (2021) shows that there may be more spindles than the ones we can see, but the less visible and 'of lower' quality spindles may not be as functionally relevant as those that are of high quality and more visible as indicated by Blanco-Duque et al. (2024). However, the current 'visibility cut-off' might still be arbitrary, potentially overlooking sleep spindles of lower quality that may still be functionally relevant.

These undetected sleep spindles may explain why we found differences between results with sleep spindle density and sigma activity. Indeed, other studies find that these measures are not perfectly correlated (R. Cox et al., 2017). Sigma activity may better capture these 'invisible' sleep spindles. In

Chapter 5, we showed that in individuals with high scores on LT, sleep spindle density and duration – but not sigma activity – are decreased during the stimulation nap compared to the baseline nap. This may suggest that infants with high scores on LT produce less high-quality sleep spindles when there is stimulation during sleep, but still have lower quality sleep spindles that are not as easily detectable. The decrease in high quality sleep spindles may be due to a decreased network synchronization due to influence of sensory input.

The future of sleep spindle research may include a transition towards data driven methods that will rely less on visual detection. This could benefit research in infant populations – with perhaps more 'invisible' sleep spindles than other populations – and will advance our understanding of the functions of sleep spindles. However, the quality of sleep spindles (which may be reflected in their visually detected number) could inform about the maturational status of the brain. In future research, a more accurate measure of sleep spindles could involve a quantification with a measure such as TFσ that captures a broader range of sleep spindle with a less arbitrary cut-off (than what the human eye can see) as well as a qualification that captures how "good" sleep spindles are, with a measure such as o-Quality.

6.2.4 Sensory influences on sleep onset and awakenings

6.2.4.1 Sensory strategies for inducing sleep onset

Sensory processing and sleep onset have a complex relationship: The transition from wake to sleep is facilitated by *increasing ánd reducing* sensory stimulation. Evading sensory stimulation, by closing your eyes or turning of the lights eases the transition to sleep. However, the opposite is also true. An infant will fall asleep to a soothing lullaby or by being rocked gently, activating the auditory and somatosensory systems respectively. Strategies used to settle an infant, including the first self-soothing strategies that infants develop, such as sucking their thumb, are often sensory in nature (Uvnäs-Moberg & Handlin, 2015).

Many of the common soothing strategies to fall asleep have been linked to oxytocin release, e.g. suckling (Lupoli et al., 2001), food intake (Ohlsson et al., 2002), mother-infant touch (Matthiesen et al., 2001), and also massage (Uvnäs-Moberg & Field, 2004). Oxytocin is known to reduced stress and anxiety, potentially inducing sleep onset. However, if sensory input is perceived as annoying by an infant, it may interfere with the development of soothing behaviours. Indeed, as shown in Chapter 2, sleep onset is both related to infant's sensory profiles, indicating heightened behavioural and affective reactivity to sensory input, as well as an infant's ability to gate tactile input. Infants with sensory differences may therefore not perceive these soothing strategies as calming.

However, it seems unlikely that this would apply to all sensory soothing strategies, as autistic individuals with sensory differences often engage in restrictive and repetitive behaviours (RRBs) that can be sensory in nature, such as watching a spinning object or flapping their hands, to calm down. It is thought that these type of behaviours help reduce the unpredictability of the environment by engaging in controlled predictable situations (Hirsh et al., 2012; Van de Cruys et al., 2014). A study in healthy fruit flies shows that sleep onset is facilitated by repetitive bursts of vibrations – similar to rocking in humans – but only if these burst are identical and thus predictable (Öztürk-Çolak et al., 2020). Therefore, the predictability of sensory input may be particularly important for sleep onset in all individuals, but perhaps even more so for those with sensory differences.

While this idea sounds plausible, it is puzzling that repetitive sensory behaviours are perceived as calming for individuals who also show reduced repetition suppression, which essentially reflects the reduced ability to accurately predict highly predictable stimuli. One possibility is that autistic individuals may particularly struggle with prediction of external sensory input, but that prediction of self-generated sensations, such as self-touch and movement, remains intact. Supporting this, a study found that neural activation to self-touch is similar between an autistic adults and non-autistic adults (Frost-Karlsson et al., 2022). Self-touch is highly predictable due to afferent proprioceptive feedback that can be used for prediction of the sensation, known as reafference (Sommer & Wurtz, 2002; von Holst & Mittelstaedt, 1950). Additionally, autistic individuals show a tendency for overreliance or preference of proprioceptive feedback signals over other signals, such as visual input, when learning a pattern (Haswell et al., 2009; Izawa et al., 2012). This may indicate that proprioceptive feedback is particularly informative for prediction purposes in autistic individuals and may be useful for sleep onset.

If infants with reduced sensory gating are more likely to calm down from self-generated sensory input, it raises the question of how they would respond to soothing methods provided by a caregiver. Would externally delivered input, such as stroking or rocking, be less effective than self-generated sensations? More research is needed to explore different soothing strategies, such as predictable vs unpredictable input or self-generated vs externally generated input, and how these approaches affect sleep onset in infants with a variety of sensory profiles.

6.2.4.2 Waking up from sensory stimulation

In Chapter 2, I demonstrated that infants at TL for autism gradually wake up less frequently between 5 and 14 months of age, consistent with research showing that most infants start sleep through the night in the first year of life (Henderson et al., 2020). In the first months of life infants wake up and sleep more irregularly throughout the day and night, which is likely linked to their feeding needs and

immature circadian rhythms (Mühlematter et al., 2023). As infants develop, the number of full-blown awakenings decrease as well as the number of brief arousals from sleep (Montemitro et al., 2008).

While waking up from sleep is often seen as sign of poor sleep, the quick reversibility of sleep is also a key sign of healthy sleep (Halász et al., 2004). Failing to wake up, especially when faced with a noxious stimulus may have detrimental consequences. For example, infants need to wake up in response to endogenous signals such as hunger or respiratory signals. This is critical because failure to arouse to those endogenous signals may have detrimental consequences, such as sudden infant death syndrome (SIDS) (Franco et al., 2010). Prospective studies of infants that will later die of SIDS show that these infants had reduced frequency of awakenings, particularly in the early morning (Kahn et al., 1992; Schechtman et al., 1992). Research in fruit flies shows that juveniles compared to adults are less likely to transition to wake once asleep, which is due to the immaturity of sleep promoting neurons and modulatory dopaminergic input (Gong et al., 2022). Therefore, decreased arousibility during sleep is a normal part infant sleep, as neuronal pathways are still maturing, but insufficient arousals may have serious consequences, highlighting a delicate balance between waking up too often and not waking up enough.

The findings of Chapter 5 show that arousal density did not increase in a nap with auditory stimulation, which may have been due to the higher likelihood of sleep protective reactions to sensory input as confirmed by the increase in K-complexes in the time-window after stimulation. Despite the shorter nap durations during the stimulation nap, infants seem to sleep well in the sleep lab, as shown by the high sleep efficiencies and the proportion of wake time during sleep in both nap conditions (>95% on average). That infants were not so disturbed by the auditory input may be due to the stimulus being innocuous. Already early in life, infants can adapt their arousal response to the saliency of a stimulus. Infants age 1 to 22 weeks gradually eliminate an arousal response to repeated tactile stimulation during sleep (McNamara et al., 1999). The elimination of the arousal response is sequential: first cortical arousals are eliminated, then brainstem responses and finally spinal responses. Even though the auditory stimulation in the SNOOSE study was presented in jittered intervals, infants may have habituated quickly due to the innocuous nature of the stimuli.

Another factor that may have contributed to low arousal rate from the stimulation is the perceived safety of the environment. As discussed in Chapter 1, the sleeping brain can adapt to the perceived level of risk in its surroundings. For example, adults exhibit a ‘first night effect’ when sleeping in an unfamiliar environment and are more reactive to sensory input that night (Agnew Jr et al., 1966; Tamaki et al., 2016). However, the ‘first night effect’ is not as prominent in infants as shown by a study in 5 week to 8 month-old infants (Rebuffat et al., 1994). They show that the structure of sleep is not

significantly different between consecutive nights in a sleep lab, which fits with the common notion that a baby can sleep anywhere. Whether infants are more reactive to stimulation during sleep in an unfamiliar environment has not been tested to my knowledge. It may be the case that for infants, perceived safety of an environment is determined less by the sleep location and more by the proximity of a caregiver. Indeed, research shows that neonates have lower heart rate variability and have significantly longer quiet sleep (the precursor of NREM sleep) when they have skin-to-skin contact with the mother compared to when they do not (Morgan et al., 2011). In the SNOOSE study, the majority of infants slept in their caregivers' arms (29 out of 41). This close contact with a caregiver may have deepened sleep due to the calming effect (Matthiesen et al., 2001) and reduced their responsiveness to the environment.

6.3 Considerations for the study of sleep and sensory processing in infancy

The SNOOSE study highlights important challenges in research on sleep and sensory processing in infancy. Here I explore key considerations for future research, including the sleep environment, participant diversity in terms of sleep and sensory symptoms and age-appropriate measures of sensory processing behaviours.

The sleep environment

In section 6.2.4.2 I discussed the influence of the sleep arrangement (whether an infant is near the parent or not) , on awakenings from sleep. This raises the question whether future infant sleep research should standardize sleeping arrangements to minimize variability in a study. Some studies already take this approach, e.g. in Sokolof et al.'s study all infants (0-6 months old) were put to sleep in a car seat. However, the feasibility of such an approach may depend on the age range of the study. In the SNOOSE study, we encouraged caregivers to use their typical settle methods to increase ecological validity. However, sleeping in a sleep lab with an EEG cap is a highly unusual environment for an infant and caregivers often engaged in settle methods they would perhaps not always use at home. Some caregivers who usually placed their infant down to nap instead held the infant in their arms during the experiment. Changes in the routine were often because the infant was upset due to the application of the sensors or because the caregiver thought the infant would not sleep otherwise in the novel environment. This strategy was very successful as only 4 out of 44 infants did not fall asleep in the lab. A solution to this would be to conduct studies in the participant's own home rather than a sleep lab. However, this brings its own practical challenges, such as technical set up, and decreased standardization of environmental factors. In the context of the SNOOSE study, background noise, an important confounding variable, may have varied significantly depending on each participant's home.

The question remains: which of the two approaches confounds the results of a study more? Is it more disruptive to change an infant's typical sleep conditions, or do the differences in sleep arrangements between participants lead to greater variability in sleep outcomes?

Recruitment of poor sleepers and sensitive infants

One key consideration for future in-lab sleep studies is the need to diversify the sample in terms of sleep and sensory profiles. In the SNOOSE study, we observed a limited variety of sensory profiles despite recruiting infants at EL for autism. Low threshold, which is assessed on a scale from 1 to 5, ranged from 1.14 to 2.73 in the SNOOSE sample. This could indicate that there may have been a self-selection process, where caregivers of highly sensitive infants may not have wanted to participate in an EEG sleep study. Indeed, some caregivers of infants at EL for autism indicated that their older autistic children would not have tolerated the EEG sensors. Compared to the BASIS dataset (see figure 5.3), the range in the SNOOSE study was much narrower, however, this may also be due to the much smaller sample size. Similarly, we may have collected a sample of exceptionally good sleepers. It is possible that only caregivers of good sleepers volunteered to participate. A potential solution to this self-selection problem could be to particularly advertise the study for infants with sensory or sleep difficulties.

Measuring sensory behaviours

When measuring behavioural and affective reactivity to sensory input, the age-appropriateness of the tasks and questions is essential. In the SNOOSE study, we noticed that some of the behaviours assessed by the Sensory Profile 2 (SP-2) may not have been suitable for all infants in our age range. As mentioned in Chapter 5 (section 5.2.5), the SP-2 has age-appropriate versions with adapted questions. The youngest version is designed for 0-7 month olds, followed by a version for 7-36 month-olds. Infants in the SNOOSE study, age 8 to 11 months-old, just falls within the latter version but are on the younger end of the 7-36 month age range.

One important feature added to the SP-2, which was not included in the ITSP, is the non-applicable option (Dunn, 2014). In the SNOOSE study, approximately half of the caregivers selected the 'non-applicable' for at least for 1 of the 23 questions. Whether this falls within typical ranges is uncertain, as to my knowledge, no studies have investigated nor reported the rates of non-applicable in their samples. In an interview with occupationaltherapy.com (accessed on 21-09-2024) Winnie Dunn explains: "*We added 'does not apply' because some of the items on the Sensory Profile™ 2 and the original Sensory Profile had behaviors that children in the vulnerable groups like autism and ADHD were much more likely to engage in, but parents of children, without those conditions, never saw those behaviors at all."* However, it is unclear why the option 'never' would not suffice to indicate behaviours

caregivers have never seen. Some questions that are left unanswered may be age-inappropriate rather than unfamiliar to the parent. For example, question Q4_9 (*"My child becomes anxious when walking or crawling on certain surfaces (for example, grass, sand, carpet, tile)"*) was indicated as non-applicable by 8/35 participants in the SNOOSE study. This may be due to the individual age differences in learning how to walk or crawl. In the SNOOSE study, the unanswered questions were excluded. However, without knowing the reason for the missing responses, it is unclear how this may skew the results. A more elaborate quantification is needed of the rates of 'non-applicable' per question in relation to age. Additional qualitative research is needed to understand why caregivers choose the 'non-applicable' option. These could help inform adaptations needed for a 3rd version of the ITSP.

6.4 Future directions

A major theme that emerged from this thesis is the importance of timescales and the difference between immediate effects and long-term effects, state-like variation and trait-like variation. Any further research should consider these aspects carefully during the design of a study and interpretation of the results.

As outlined in the introduction, both sleep and sensory processing are broad constructs, which consist of multiple subcomponents. The recently proposed taxonomy of He et al. (2023) highlights the complexity of what it means to have 'sensory differences'. The studies presented in this thesis confirm that various sensory processing measures may capture entirely separate concepts. It is still largely unclear how measures at different levels of sensory processing are related, although some studies have begun to investigate this (Kisley et al., 2004; M. W. M. Kuiper et al., 2019). Moreover, to what extent sensory measures represent trait- or state-like variation is largely unknown. For example, in the case of sensory gating, one study in healthy adults looked at the test-retest reliability of sensory gating of auditory input, measured as the difference of P50 response to S1 and S2 (Fuerst et al., 2007). They measured sensory gating twice on the same day and found a moderately high correlation (r=.610). Understanding how much daily or even hourly fluctuation there is in measurements is important to understand the relationship with sleep measures. The degree of variability across multiple nights is better established for sleep variables (De Gennaro et al., 2005). As proposed in Chapter 3, an intensive longitudinal study that measures sleep and sensory processing on a daily basis for multiple days could help clarify the directionality of sensory differences and sleep, as well the stability of measures. Recent advances in wearables to measure sleep at home, such as actigraphy or EEG headbands (González et al., 2024), make such studies more feasible. Intensive longitudinal studies with actigraphy are also feasible in infants and can monitor both daytime and nighttime sleep (Schoch et al., 2021).

Our finding that infants with heightened sensory profiles exhibit lower SWA should be explored further. One intriguing avenue for future research would be to investigate whether increasing SWA improves sensory responses the next day. One way to enhance SWA is through auditory closed loop stimulation. Additionally, this could inform about whether SWs react similarly to auditory closed loop stimulation in individuals with sensory differences. In elderly people, for example, auditory closed loop stimulation had minimal effects on SWA and did not enhance memory performance the next day (J. Schneider et al., 2020). It is therefore unclear whether atypical populations react similarly to auditory closed loop stimulation. Furthermore, the effects are of having lower SWA than others should be explored. It is not fully understood whether lower SWA has a significant impact on daily functioning and further development.

In Chapter 5, we looked at the effects of simple, non-salient auditory input. Another line of research could build on thus by investigating the effects of the saliency of stimulation before and during sleep on infant sleep. These stimuli could be more ecologically valid, such as emotional speech or unfamiliar voices. Three-month-old infants are already able to distinguish a familiar from an unfamiliar voice. Studies in adults show enhanced responses during sleep to unfamiliar voices over familiar voices and emotional over unemotional tones (Ameen et al., 2022; Blume et al., 2017). Additionally, sensory gating during sleep onset itself could be explored in relation to how quickly infants fall asleep. This could further clarify our finding that sensory gating and sleep onset latency are related.

6.5 Conclusion

In this thesis, I investigated whether sensory processing differences lead to sleep difficulties, due to poor gating mechanisms of sensory input. We tested this in infants at elevated and typical likelihood for autism who have a variety of sensory profiles. In our first study, we found for the first time that an objective measure of sensory gating associates with sleep onset, with poor gating predicting longer sleep onset times at 10 months of age. We then investigated temporal precedence, using a longitudinal study design from 5 to 14 months, this time with a parental-reported measure of an infant's sensory behaviours. We did not find any evidence that early sensory profiles predict changes in later sleep. Instead, we found that over the course of the study infants that in general wake up frequently at night also tend to have heightened sensory profiles, suggestive of a common mechanism driving both. We then looked at the effect of sensory input – simple auditory tones - on sleep in infants with a variety of sensory profiles. We found that sleep protective markers are linked to sensory profiles. Specifically, an infant's sensory profile, as assessed by caregiver report, associates with objective measures of sleep depth, irrespective of the sensory environment. Additionally, sensory input may disrupt sleep spindle production in infants that have heightened sensory profiles.

Taken together these findings suggest that already early in development sensory differences and sleep are entangled. Our findings indicate that a common underlying mechanism may drive both sleep and sensory differences. In addition, sensory differences may drive sleep difficulties on shorter timescales. Further studies should investigate day-to-day variations in sleep and sensory differences. The studies in this thesis give some indications of why sleep and sensory processing differences often co-occur, but give rise to many more questions. Importantly, we show that the terms ‘sleep’ and ‘sensory processing’ need to be disentangled if we want to understand the nature of their relationship.

References

Ackermann, S., Hartmann, F., Papassotiropoulos, A., de Quervain, D. J. F., & Rasch, B. (2015). No Associations between Interindividual Differences in Sleep Parameters and Episodic Memory Consolidation. *Sleep*, *38*(6), 951–959. https://doi.org/10.5665/sleep.4748

Adamantidis, A. R., Gutierrez Herrera, C., & Gent, T. C. (2019). Oscillating circuitries in the sleeping brain. *Nature Reviews Neuroscience*, *20*(12), 746–762. https://doi.org/10.1038/s41583-019-0223-4

Agnew Jr, H., Webb, W. B., & Williams, R. L. (1966). The first night effect: An Eeg study of sleep. *Psychophysiology*, *2*(3), 263–266.

Agosto, J., Choi, J. C., Parisky, K. M., Stilwell, G., Rosbash, M., & Griffith, L. C. (2008). Modulation of GABAA receptor desensitization uncouples sleep onset and maintenance in Drosophila. *Nature Neuroscience*, *11*(3), 354–359. https://doi.org/10.1038/nn2046

Ameen, M. S., Heib, D. P. J., Blume, C., & Schabus, M. (2022). The Brain Selectively Tunes to Unfamiliar Voices during Sleep. *The Journal of Neuroscience*, *42*(9), 1791. https://doi.org/10.1523/JNEUROSCI.2524-20.2021

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th edition). American Psychiatric Publishing.

Amzica, F., & Steriade, M. (1995). Short-and long-range neuronal synchronization of the slow (< 1 Hz) cortical oscillation. *Journal of Neurophysiology*, *73*(1), 20–38.

Amzica, F., & Steriade, M. (2002). The functional significance of K-complexes. *Sleep Medicine Reviews*, *6*(2), 139–149.

Anderson, J. C., & Gerbing, D. W. (1984). The effect of sampling error on convergence, improper solutions, and goodness-of-fit indices for maximum likelihood confirmatory factor analysis. *Psychometrika*, *49*, 155–173.

Andrillon, T., Burns, A., Mackay, T., Windt, J., & Tsuchiya, N. (2021). Predicting lapses of attention with sleep-like slow waves. *Nature Communications*, *12*(1), 3657. https://doi.org/10.1038/s41467-021-23890-7

Andrillon, T., & Kouider, S. (2020). The vigilant sleeper: Neural mechanisms of sensory (de)coupling during sleep. *Current Opinion in Physiology*, *15*, 47–59. Scopus. https://doi.org/10.1016/j.cophys.2019.12.002

Andrillon, T., Poulsen, A. T., Hansen, L. K., Léger, D., & Kouider, S. (2016). Neural Markers of Responsiveness to the Environment in Human Sleep. *The Journal of Neuroscience*, *36*(24), 6583. https://doi.org/10.1523/JNEUROSCI.0902-16.2016

Appleyard, K., Schaughency, E., Taylor, B., Sayers, R., Haszard, J., Lawrence, J., Taylor, R., & Galland, B. (2020). Sleep and Sensory Processing in Infants and Toddlers: A Cross-Sectional and Longitudinal Study. *American Journal of Occupational Therapy*, *74*(6), 7406205010p1-7406205010p12. https://doi.org/10.5014/ajot.2020.038182

Araujo, P., Coelho, C. A., Oliveira, M. G., Tufik, S., & Andersen, M. L. (2018). Neonatal sleep restriction increases nociceptive sensitivity in adolescent mice. *Pain Physician*, *21*(2), E137.

Arazi, A., Meiri, G., Danan, D., Michaelovski, A., Flusser, H., Menashe, I., Tarasiuk, A., & Dinstein, I. (2020). Reduced sleep pressure in young children with autism. *Sleep*, *43*(6), zsz309. https://doi.org/10.1093/sleep/zsz309

Atun-Einy, O., & Scher, A. (2016). Sleep disruption and motor development: Does pulling-to-stand impacts sleep–wake regulation? *Infant Behavior and Development*, *42*, 36–44.

Baayen, R. H., Davidson, D. J., & Bates, D. M. (2008). Mixed-effects modeling with crossed random effects for subjects and items. *Special Issue: Emerging Data Analysis*, *59*(4), 390–412. https://doi.org/10.1016/j.jml.2007.12.005

Bal, T., & McCormick, D. A. (1996). What Stops Synchronized Thalamocortical Oscillations? *Neuron*, *17*(2), 297–308. https://doi.org/10.1016/S0896-6273(00)80161-0

Baranek, G. T., Carlson, M., Sideris, J., Kirby, A. V., Watson, L. R., Williams, K. L., & Bulluck, J. (2019). Longitudinal assessment of stability of sensory features in children with autism spectrum disorder or other developmental disabilities. *Autism Research*, *12*(1), 100–111.

Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., & Clubley, E. (2001). The Autism-Spectrum Quotient (AQ): Evidence from Asperger Syndrome/High-Functioning Autism, Males and Females, Scientists and Mathematicians. *Journal of Autism and Developmental Disorders*, *31*(1), 5–17. https://doi.org/10.1023/A:1005653411471

Bartho, P., Slezia, A., Matyas, F., Faradzs-Zade, L., Ulbert, I., Harris, K. D., & Acsady, L. (2014). Ongoing network state controls the length of sleep spindles via inhibitory activity. *Neuron*, *82*(6), 1367–1379.

Bastien, C., & Campbell, K. (1992). The Evoked K-Complex: All-or-None Phenomenon? *Sleep*, *15*(3), 236–245. https://doi.org/10.1093/sleep/15.3.236

Beaugrand, M., Jaramillo, V., Markovic, A., Huber, R., Kohler, M., Schoch, S. F., & Kurth, S. (2023). Lack of association between behavioral development and simplified topographical markers of the sleep EEG in infancy. *Neurobiology of Sleep and Circadian Rhythms*, *15*, 100098. https://doi.org/10.1016/j.nbscr.2023.100098

Beck, J., Loretz, E., & Rasch, B. (2021). Exposure to relaxing words during sleep promotes slow-wave sleep and subjective sleep quality. *Sleep*, *44*(11), zsab148. https://doi.org/10.1093/sleep/zsab148

Begum-Ali, J., Gossé, L. K., Mason, L., Pasco, G., Charman, T., Johnson, M. H., Jones, E. J. H., & The STAARS Team. (2023). Infant sleep predicts trajectories of social attention and later autism traits. *Journal of Child Psychology and Psychiatry*, *64*(8), 1200–1211. https://doi.org/10.1111/jcpp.13791

Bellesi, M., Riedner, B. A., Garcia-Molina, G. N., Cirelli, C., & Tononi, G. (2014). Enhancement of sleep slow waves: Underlying mechanisms and practical consequences. *Frontiers in Systems Neuroscience*, *8*. https://www.frontiersin.org/article/10.3389/fnsys.2014.00208

Ben-Sasson, A., Gal, E., Fluss, R., Katz-Zetler, N., & Cermak, S. A. (2019). Update of a Meta-analysis of Sensory Symptoms in ASD: A New Decade of Research. *Journal of Autism and Developmental Disorders*, *49*(12), 4974–4996. https://doi.org/10.1007/s10803-019-04180-0

Berja, E. D., Kwon, H., Walsh, K. G., Bates, S. V., Kramer, M. A., & Chu, C. J. (2024). Infant sleep spindle measures from EEG improve prediction of cerebral palsy. *Clinical Neurophysiology*, *167*, 51–60. https://doi.org/10.1016/j.clinph.2024.08.017

Berry, D., & Willoughby, M. T. (2017). On the Practical Interpretability of Cross-Lagged Panel Models: Rethinking a Developmental Workhorse. *Child Development*, *88*(4), 1186–1206. https://doi.org/10.1111/cdev.12660

Blanco-Duque, C., Bond, S. A., Krone, L. B., Dufour, J.-P., Gillen, E. C. P., Purple, R. J., Kahn, M. C., Bannerman, D. M., Mann, E. O., Achermann, P., Olbrich, E., & Vyazovskiy, V. V. (2024). Oscillatory-Quality of sleep spindles links brain state with sleep regulation and function. *Science Advances*, *10*(36), eadn6247. https://doi.org/10.1126/sciadv.adn6247

Blumberg, M. S., Marques, H. G., & Iida, F. (2013). Twitching in Sensorimotor Development from Sleeping Rats to Robots. *Current Biology*, *23*(12), R532–R537. https://doi.org/10.1016/j.cub.2013.04.075

Blume, C., del Giudice, R., Lechinger, J., Wislowska, M., Heib, D. P. J., Hoedlmoser, K., & Schabus, M. (2017). Preferential processing of emotionally and self-relevant stimuli persists in unconscious N2 sleep. *Sleep and Language Learning*, *167*, 72–82. https://doi.org/10.1016/j.bandl.2016.02.004

Blume, C., del Giudice, R., Wislowska, M., Heib, D. P. J., & Schabus, M. (2018). Standing sentinel during human sleep: Continued evaluation of environmental stimuli in the absence of consciousness. *NeuroImage*, *178*, 638–648. https://doi.org/10.1016/j.neuroimage.2018.05.056

Blume, C., Schoch, S., Vienneau, D., Röösli, M., Kohler, M., Moeller, A., Kurth, S., & Usemann, J. (2021). Association of transportation noise with sleep during the first year of life: A longitudinal study. *Environmental Research*, *203*, 111776. https://doi.org/10.1016/j.envres.2021.111776

Bollen, K. A. (1987). Outliers and Improper Solutions: A Confirmatory Factor Analysis Example. *Sociological Methods & Research*, *15*(4), 375–384. https://doi.org/10.1177/0049124187015004002

Bölte, S., Holtmann, M., & Poustka, F. (2008). The social communication questionnaire (SCQ) as a screener for autism spectrum disorders: Additional evidence and cross-cultural validity. *Journal of the American Academy of Child & Adolescent Psychiatry*, *47*(6), 719–720. https://doi.org/10.1097/CHI.0b013e31816c42bd

Bonett, M. (1985). The effect of sleep disruption on performance, sleep and mood. *Sleep*, *8*(11).

Bonnel, A., Mottron, L., Peretz, I., Trudel, M., Gallun, E., & Bonnel, A.-M. (2003). Enhanced pitch sensitivity in individuals with autism: A signal detection analysis. *Journal of Cognitive Neuroscience*, *15*(2), 226–235.

Bonnet, M. H., Johnson, L. C., & Webb, W. B. (1978). The Reliability of Arousal Threshold During Sleep. *Psychophysiology*, *15*(5), 412–416. https://doi.org/10.1111/j.1469-8986.1978.tb01407.x

Borbély, A. A. (1982). A two process model of sleep regulation. *Hum Neurobiol*, *1*(3), 195–204.

Born, J., & Wilhelm, I. (2012). System consolidation of memory during sleep. *Psychological Research*, *76*, 192–203.

Boucher, J., & Anns, S. (2018). Memory, learning and language in autism spectrum disorder. *Autism & Developmental Language Impairments*, *3*, 2396941517742078. https://doi.org/10.1177/2396941517742078

Bourdet, C., & Goldenberg, F. (1994). Insomnia in anxiety: Sleep EEG changes. *Journal of Psychosomatic Research*, *38*, 93–104. https://doi.org/10.1016/0022-3999(94)90140-6

Bourgeron, T. (2015). From the genetic architecture to synaptic plasticity in autism spectrum disorder. *Nature Reviews Neuroscience*, *16*(9), 551–563.

Briggs, F., & Usrey, W. M. (2008). Emerging views of corticothalamic function. *Sensory Systems*, *18*(4), 403–407. https://doi.org/10.1016/j.conb.2008.09.002

Buckley, T. M., & Schatzberg, A. F. (2005). On the Interactions of the Hypothalamic-Pituitary-Adrenal (HPA) Axis and Sleep: Normal HPA Axis Activity and Circadian Rhythm, Exemplary Sleep Disorders. *The Journal of Clinical Endocrinology & Metabolism*, *90*(5), 3106–3114. https://doi.org/10.1210/jc.2004-1056

Bullmore, E. T., Suckling, J., Overmeyer, S., Rabe-Hesketh, S., Taylor, E., & Brammer, M. J. (1999). Global, voxel, and cluster tests, by theory and permutation, for a difference between two groups of structural MR images of the brain. *IEEE Transactions on Medical Imaging*, *18*(1), 32–42.

Burnham, M. M., Goodlin-Jones, B. L., Gaylor, E. E., & Anders, T. F. (2002). Nighttime sleep-wake patterns and self-soothing from birth to one year of age: A longitudinal intervention study. *Journal of Child Psychology and Psychiatry*, *43*(6), 713–725. https://doi.org/10.1111/1469-7610.00076

Camerota, M., Propper, C. B., & Teti, D. M. (2019). Intrinsic and extrinsic factors predicting infant sleep: Moving beyond main effects. *Developmental Review*, *53*. https://doi.org/10.1016/j.dr.2019.100871

Campbell, K. (2010). Event-related potentials as a measure of sleep disturbance: A tutorial review. *Noise and Health*, *12*(47), 137.

Carcea, I., & Froemke, R. C. (2013). Chapter 3—Cortical Plasticity, Excitatory–Inhibitory Balance, and Sensory Perception. In M. M. Merzenich, M. Nahum, & T. M. Van Vleet (Eds.), *Progress in Brain Research* (Vol. 207, pp. 65–90). Elsevier. https://doi.org/10.1016/B978-0-444-63327-9.00003-5

Cardis, R., Lecci, S., Fernandez, L. M., Osorio-Forero, A., Chu Sin Chung, P., Fulda, S., Decosterd, I., & Lüthi, A. (2021). Cortico-autonomic local arousals and heightened somatosensory arousability during NREMS of mice in neuropathic pain. *eLife*, *10*, e65835. https://doi.org/10.7554/eLife.65835

Carter Leno, V., Wright, N., Pickles, A., Bedford, R., Zaidman-Zait, A., Kerns, C., Mirenda, P., Zwaigenbaum, L., Duku, E., Bennett, T., Georgiades, S., Smith, I., Vaillancourt, T., Szatmari, P., & Elsabbagh, M. (2022). Exposure to family stressful life events in autistic children: Longitudinal associations with mental health and the moderating role of cognitive flexibility. *Autism*, *26*(7), 1656–1667. https://doi.org/10.1177/13623613211061932

Cartwright, N. (2007). *Hunting causes and using them: Approaches in philosophy and economics*. Cambridge University Press.

Cary, E., Pacheco, D., Kaplan-Kahn, E., McKernan, E., Matsuba, E., Prieve, B., & Russo, N. (2024). Brain Signatures of Early and Late Neural Measures of Auditory Habituation and Discrimination in Autism and Their Relationship to Autistic Traits and Sensory Overresponsivity. *Journal of Autism and Developmental Disorders*, *54*(4), 1344–1360. https://doi.org/10.1007/s10803-022-05866-8

Chamak, B., Bonniau, B., Jaunay, E., & Cohen, D. (2008). What can we learn about autism from autistic persons? *Psychotherapy and Psychosomatics*, *77*(5), 271–279.

Chang, M. C., Parham, L. D., Blanche, E. I., Schell, A., Chou, C.-P., Dawson, M., & Clark, F. (2012). Autonomic and Behavioral Responses of Children With Autism to Auditory Stimuli. *The American Journal of Occupational Therapy*, *66*(5), 567–576. https://doi.org/10.5014/ajot.2012.004242

Chawner, S. J. R. A., Evans, A., Wolstencroft, J., Chawner, S. J. R. A., Hall, J., van den Bree, M. B. M., Owen, M. J., Skuse, D., Raymond, F. L., Williams, N., Owen, M. J., Hall, J., van den Bree, M. B. M., & IMAGINE-ID consortium. (2023). Sleep disturbance as a transdiagnostic marker of psychiatric risk in children with neurodevelopmental risk genetic conditions. *Translational Psychiatry*, *13*(1), 7. https://doi.org/10.1038/s41398-022-02296-z

Chegodaev, D., Pavlova, P., & Kiselev, S. (2022). More than just immaturity: Evidence supporting the hypothesis that sleep spindle characteristics reflect GABAergic depolarization in infancy. *Sleep Science*, *15*(4), 459.

Chen, A., Peter, V., & Burnham, D. (2016). Auditory ERP response to successive stimuli in infancy. *PeerJ*, *4*, e1580. https://doi.org/10.7717/peerj.1580

Chen, Z., Wimmer, R. D., Wilson, M. A., & Halassa, M. M. (2016). Thalamic Circuit Mechanisms Link Sensory Processing in Sleep and Attention. *Frontiers in Neural Circuits*, *9*, 83–83. PubMed. https://doi.org/10.3389/fncir.2015.00083

Chevance, G., Baretta, D., Romain, A. J., Godino, J. G., & Bernard, P. (2022). Day-to-day associations between sleep and physical activity: A set of person-specific analyses in adults with overweight and obesity. *Journal of Behavioral Medicine*, *45*(1), 14–27.

Chilakamarri, P., Thurm, A., Farmer, C., Swedo, S., Burroughs, S. A., Holmes, G. L., & Buckley, A. W. (2017). Characterizing Sleep Spindles in Children with Autism Spectum Disorder (ASD), Developmental Delay and Neurotypical Development. (P3.209). *Neurology*, *88*(16 Supplement), P3.209.

Cigánek, L. (1961). The EEG response (evoked potential) to light stimulus in man. *Electroencephalography and Clinical Neurophysiology*, *13*(2), 165–172. https://doi.org/10.1016/0013-4694(61)90132-8

Cirelli, C. (2013). Sleep and synaptic changes. *Current Opinion in Neurobiology*, *23*(5), 841–846.

Claude, L., Chouchou, F., Prados, G., Castro, M., De Blay, B., Perchet, C., García-Larrea, L., Mazza, S., & Bastuji, H. (2015). Sleep spindles and human cortical nociception: A surface and intracerebral electrophysiological study. *The Journal of Physiology*, *593*(22), 4995–5008.

Coenen, A. (2024). Sensory gating and gaining in sleep: The balance between the protection of sleep and the safeness of life (a review). *Journal of Sleep Research*, *33*(5), e14152. https://doi.org/10.1111/jsr.14152

Coenen, A., & Vendrik, A. J. H. (1972). Determination of the transfer ratio of cat's geniculate neurons through quasi-intracellular recordings and the relation with the level of alertness. *Experimental Brain Research*, *14*(3), 227–242. https://doi.org/10.1007/BF00816160

Coghlan, S., Horder, J., Inkster, B., Mendez, M. A., Murphy, D. G., & Nutt, D. J. (2012). GABA system dysfunction in autism and related disorders: From synapse to symptoms. *Neuroscience and Biobehavioral Reviews*, *36*(9), 2044–2055. PubMed. https://doi.org/10.1016/j.neubiorev.2012.07.005

Cohen, M. X. (2014). *Analyzing neural time series data: Theory and practice*. MIT press.

Cohen, S., Conduit, R., Lockley, S. W., Rajaratnam, S. M., & Cornish, K. M. (2014). The relationship between sleep and behavior in autism spectrum disorder (ASD): A review. *Journal of Neurodevelopmental Disorders*, *6*(1), 44. https://doi.org/10.1186/1866-1955-6-44

Colonnese, M. T., Kaminska, A., Minlebaev, M., Milh, M., Bloem, B., Lescure, S., Moriette, G., Chiron, C., Ben-Ari, Y., & Khazipov, R. (2010). A conserved switch in sensory processing prepares developing neocortex for vision. *Neuron*, *67*(3), 480–498.

Colrain, I. M. (2005). The K-Complex: A 7-Decade History. *Sleep*, *28*(2), 255–273. https://doi.org/10.1093/sleep/28.2.255

Combrisson, E., Vallat, R., Eichenlaub, J.-B., O'Reilly, C., Lajnef, T., Guillot, A., Ruby, P. M., & Jerbi, K. (2017). Sleep: An Open-Source Python Software for Visualization, Analysis, and Staging of Sleep Data. *Frontiers in Neuroinformatics*, *11*. https://www.frontiersin.org/article/10.3389/fninf.2017.00060

Combrisson, E., Vallat, R., O'Reilly, C., Jas, M., Pascarella, A., Saive, A., Thiery, T., Meunier, D., Altukhov, D., Lajnef, T., Ruby, P., Guillot, A., & Jerbi, K. (2019). Visbrain: A Multi-Purpose GPU-Accelerated Open-Source Suite for Multimodal Brain Data Visualization. *Frontiers in Neuroinformatics*, *13*. https://www.frontiersin.org/articles/10.3389/fninf.2019.00014

Cook, F., Conway, L. J., Giallo, R., Gartland, D., Sciberras, E., & Brown, S. (2020). Infant sleep and child mental health: A longitudinal investigation. *Archives of Disease in Childhood*, *105*(7), 655. https://doi.org/10.1136/archdischild-2019-318014

Coppieters 't Wallant, D., Maquet, P., & Phillips, C. (2016). Sleep Spindles as an Electrographic Element: Description and Automatic Detection Methods. *Neural Plasticity*, *2016*, 6783812. https://doi.org/10.1155/2016/6783812

Cordi, M. J., Ackermann, S., & Rasch, B. (2019). Effects of relaxing music on healthy sleep. *Scientific Reports*, *9*(1), 9079.

Cortese, S., Faraone, S. V., Konofal, E., & Lecendreux, M. (2009). Sleep in children with attention-deficit/hyperactivity disorder: Meta-analysis of subjective and objective studies. *Journal of the American Academy of Child & Adolescent Psychiatry*, *48*(9), 894–908.

Cox, J., Pinto, L., & Dan, Y. (2016). Calcium imaging of sleep-wake related neuronal activity in the dorsal pons. *Nature Communications*, *7*, 10763–10763. PubMed. https://doi.org/10.1038/ncomms10763

Cox, R., Schapiro, A. C., Manoach, D. S., & Stickgold, R. (2017). Individual Differences in Frequency and Topography of Slow and Fast Sleep Spindles. *Frontiers in Human Neuroscience*, *11*. https://www.frontiersin.org/articles/10.3389/fnhum.2017.00433

Crabtree, J. W. (1999). Intrathalamic sensory connections mediated by the thalamic reticular nucleus. *Cellular and Molecular Life Sciences CMLS*, *56*(7), 683–700. https://doi.org/10.1007/s000180050462

Crowley, S. J., Wolfson, A. R., Tarokh, L., & Carskadon, M. A. (2018). An update on adolescent sleep: New evidence informing the perfect storm model. *Journal of Adolescence*, *67*, 55–65. https://doi.org/10.1016/j.adolescence.2018.06.001

Crupi, D., Hulse, B. K., Peterson, M. J., Huber, R., Ansari, H., Coen, M., Cirelli, C., Benca, R. M., Ghilardi, M. F., & Tononi, G. (2009). Sleep-Dependent Improvement in Visuomotor Learning: A Causal Role for Slow Waves. *Sleep*, *32*(10), 1273–1284. https://doi.org/10.1093/sleep/32.10.1273

Cullen, L. A., Barlow, J. H., & Cushway, D. (2005). Positive touch, the implications for parents and their children with autism: An exploratory study. *Complementary Therapies in Clinical Practice*, *11*(3), 182–189.

Curran, P. J., & Hancock, G. R. (2021). The challenge of modeling co-developmental processes over time. *Child Development Perspectives*, *15*(2), 67–75.

Curran, P. J., Howard, A. L., Bainter, S. A., Lane, S. T., & McGinley, J. S. (2014). The separation of between-person and within-person components of individual change over time: A latent curve model with structured residuals. *Journal of Consulting and Clinical Psychology*, *82*, 879–894. https://doi.org/10.1037/a0035297

Dalsgaard, M. K., & Secher, N. H. (2007). The brain at work: A cerebral metabolic manifestation of central fatigue? *Journal of Neuroscience Research*, *85*(15), 3334–3339.

Dan, B., & Boyd, S. G. (2006). A neurophysiological perspective on sleep and its maturation. *Developmental Medicine & Child Neurology*, *48*(9), 773–779. https://doi.org/10.1111/j.1469-8749.2006.tb01366.x

D'Atri, A., Novelli, L., Ferrara, M., Bruni, O., & De Gennaro, L. (2018). Different maturational changes of fast and slow sleep spindles in the first four years of life. *Sleep Medicine*, *42*, 73–82. https://doi.org/10.1016/j.sleep.2017.11.1138

David, F., Schmiedt, J. T., Taylor, H. L., Orban, G., Di Giovanni, G., Uebele, V. N., Renger, J. J., Lambert, R. C., Leresche, N., & Crunelli, V. (2013). Essential thalamic contribution to slow waves of natural sleep. *Journal of Neuroscience*, *33*(50), 19599–19610.

Davies, R., Belt, P., Roberts, S., Ali, N., & Stradling, J. (1993). Arterial blood pressure responses to graded transient arousal from sleep in normal humans. *Journal of Applied Physiology*, *74*(3), 1123–1130.

De Gennaro, L., Ferrara, M., & Bertini, M. (2000). The spontaneous K-complex during stage 2 sleep: Is it the 'forerunner'of delta waves? *Neuroscience Letters*, *291*(1), 41–43.

De Gennaro, L., Ferrara, M., Vecchio, F., Curcio, G., & Bertini, M. (2005). An electroencephalographic fingerprint of human sleep. *NeuroImage*, *26*(1), 114–122. https://doi.org/10.1016/j.neuroimage.2005.01.020

de Groot, E. R., Dudink, J., & Austin, T. (2024). Sleep as a driver of pre- and postnatal brain development. *Pediatric Research*. https://doi.org/10.1038/s41390-024-03371-5

De Laet, A., Piccardi, E. S., Begum-Ali, J., Charman, T., Johnson, M. H., Jones, E. J. H., Bedford, R., Gliga, T., Agyapong, M., Bazelmans, T., Dafner, L., Ersoy, M., Goodwin, A., Haartsen, R., Halkola, H., Hendry, A., Holman, R., Kalwarowsky, S., Kolesnik-Taylor, A., … The STAARS Team. (2022). Neuronal gating of tactile input and sleep in 10-month-old infants at typical and elevated likelihood for autism spectrum disorder. *Scientific Reports*, *12*(1), 14188. https://doi.org/10.1038/s41598-022-18018-w

Deliens, G., & Peigneux, P. (2019). Sleep–behaviour relationship in children with autism spectrum disorder: Methodological pitfalls and insights from cognition and sensory processing. *Developmental Medicine & Child Neurology*, *61*(12), 1368–1376. https://doi.org/10.1111/dmcn.14235

Dell'Osso, L., Massoni, L., Battaglini, S., Cremone, I. M., Carmassi, C., & Carpita, B. (2022). Biological correlates of altered circadian rhythms, autonomic functions and sleep problems in autism spectrum disorder. *Annals of General Psychiatry*, *21*(1), 13. https://doi.org/10.1186/s12991-022-00390-6

Dereymaeker, A., Pillay, K., Vervisch, J., De Vos, M., Van Huffel, S., Jansen, K., & Naulaers, G. (2017). Review of sleep-EEG in preterm and term neonates. *Early Human Development*, *113*, 87–103. https://doi.org/10.1016/j.earlhumdev.2017.07.003

Dias, C. C., Figueiredo, B., & Pinto, T. M. (2018). Children's Sleep Habits Questionnaire – Infant Version. *Jornal de Pediatria*, *94*(2), 146–154. https://doi.org/10.1016/j.jped.2017.05.012

Diedenhofen, B., & Musch, J. (2015). cocor: A Comprehensive Solution for the Statistical Comparison of Correlations. *PLOS ONE*, *10*(4), e0121945. https://doi.org/10.1371/journal.pone.0121945

Dijk, D. J., Beersma, D. G., & Daan, S. (1987). EEG power density during nap sleep: Reflection of an hourglass measuring the duration of prior wakefulness. *Journal of Biological Rhythms*, *2*(3), 207–219.

Dijk, D. J., Brunner, D. P., Beersma, D. G. M., & Borbély, A. A. (1990). Electroencephalogram Power Density and Slow Wave Sleep as a Function of Prior Waking and Circadian Phase. *Sleep*, *13*(5), 430–440. https://doi.org/10.1093/sleep/13.5.430

Dill, D., Adolph, E., & Wilber, C. (1964). *Handbook of physiology. Section 4. Adaptation to the environment.*

Dillon, W. R., Kumar, A., & Mulani, N. (1987). Offending estimates in covariance structure analysis: Comments on the causes of and solutions to Heywood cases. *Psychological Bulletin*, *101*(1), 126–135. https://doi.org/10.1037/0033-2909.101.1.126

Dimitrov, T., He, M., Stickgold, R., & Prerau, M. J. (2021). Sleep spindles comprise a subset of a broader class of electroencephalogram events. *Sleep*, *44*(9), zsab099. https://doi.org/10.1093/sleep/zsab099

Doldur-Balli, F., Imamura, T., Veatch, O. J., Gong, N. N., Lim, D. C., Hart, M. P., Abel, T., Kayser, M. S., Brodkin, E. S., & Pack, A. I. (2022). Synaptic dysfunction connects autism spectrum disorder and sleep disturbances: A perspective from studies in model organisms. *Sleep Medicine Reviews*, *62*, 101595. https://doi.org/10.1016/j.smrv.2022.101595

Dooley, J. C., Sokoloff, G., & Blumberg, M. S. (2019). Behavioral states modulate sensory processing in early development. *Current Sleep Medicine Reports*, *5*, 112–117.

Dressle, R. J., Feige, B., Spiegelhalder, K., Schmucker, C., Benz, F., Mey, N. C., & Riemann, D. (2022). HPA axis activity in patients with chronic insomnia: A systematic review and meta-analysis of case–control studies. *Sleep Medicine Reviews*, *62*, 101588. https://doi.org/10.1016/j.smrv.2022.101588

Dunn, W. (2002). *Infant/Toddler Sensory Profile manual*. Psychological Corporation.

Dunn, W. (2014). *Sensory Profile 2: User's Manual*. Psych Corporation. https://books.google.co.uk/books?id=rxrhoQEACAAJ

Dwyer, P., Saron, C. D., & Rivera, S. M. (2020). Identification of Longitudinal Sensory Subtypes in Typical Development and Autism Spectrum Development Using Growth Mixture Modelling. *Research in Autism Spectrum Disorders*, *78*, 101645. https://doi.org/10.1016/j.rasd.2020.101645

Ellingson, R. J. (1982). Development of sleep spindle bursts during the first year of life. *Sleep*, *5*(1), 39–46.

Ellingson, R. J., & Peters, J. F. (1980). Development of EEG and daytime sleep patterns in normal full-term infants during the first 3 months of life: Longitudinal observations. *Electroencephalography and Clinical Neurophysiology*, *49*(1–2), 112–124.

Engel-Yeger, B., & Shochat, T. (2012). The Relationship between Sensory Processing Patterns and Sleep Quality in Healthy Adults. *Canadian Journal of Occupational Therapy*, *79*(3), 134–141. https://doi.org/10.2182/cjot.2012.79.3.2

Ermis, U., Krakow, K., & Voss, U. (2010). Arousal thresholds during human tonic and phasic REM sleep. *Journal of Sleep Research*, *19*(3), 400–406. https://doi.org/10.1111/j.1365-2869.2010.00831.x

Esser, S. K., Hill, S. L., & Tononi, G. (2007). Sleep Homeostasis and Cortical Synchronization: I. Modeling the Effects of Synaptic Strength on Sleep Slow Waves. *Sleep*, *30*(12), 1617–1630. https://doi.org/10.1093/sleep/30.12.1617

Esser, S. K., Hill, S., & Tononi, G. (2009). Breakdown of effective connectivity during slow wave sleep: Investigating the mechanism underlying a cortical gate using large-scale modeling. *Journal of Neurophysiology*, *102*(4), 2096–2111.

Estes, A., Munson, J., Dawson, G., Koehler, E., Zhou, X.-H., & Abbott, R. (2009). Parenting stress and psychological functioning among mothers of preschool children with autism and developmental delay. *Autism*, *13*(4), 375–387.

Estes, A., Zwaigenbaum, L., Gu, H., St. John, T., Paterson, S., Elison, J. T., Hazlett, H., Botteron, K., Dager, S. R., & Schultz, R. T. (2015). Behavioral, cognitive, and adaptive development in infants with autism spectrum disorder in the first 2 years of life. *Journal of Neurodevelopmental Disorders*, *7*, 1–10.

Eyuboglu, M., & Eyuboglu, D. (2020). Sensory reactivity and sleep problems in toddlers with autism spectrum disorder and anxiety/depression symptoms in their mothers: Are they related? *Early Child Development and Care*, *190*(11), 1791–1801. https://doi.org/10.1080/03004430.2018.1550750

Fabrizi, L., Slater, R., Worley, A., Meek, J., Boyd, S., Olhede, S., & Fitzgerald, M. (2011). A shift in sensory processing that enables the developing human brain to discriminate touch from pain. *Current Biology*, *21*(18), 1552–1558.

Farmer, C. A., Chilakamarri, P., Thurm, A. E., Swedo, S. E., Holmes, G. L., & Buckley, A. W. (2018). Spindle activity in young children with autism, developmental delay, or typical development. *Neurology*, *91*(2), e112. https://doi.org/10.1212/WNL.0000000000005759

Fasiello, E., Gorgoni, M., Galbiati, A., Sforza, M., Berra, F., Scarpelli, S., Alfonsi, V., Annarumma, L., Casoni, F., Zucconi, M., Castronovo, V., Ferini-Strambi, L., & De Gennaro, L. (2024). Decreased Delta/Beta ratio index as the sleep state-independent electrophysiological signature of sleep state misperception in Insomnia disorder: A focus on the sleep onset and the whole night. *NeuroImage*, *298*, 120782. https://doi.org/10.1016/j.neuroimage.2024.120782

Fattinger, S., Jenni, O. G., Schmitt, B., Achermann, P., & Huber, R. (2014). Overnight Changes in the Slope of Sleep Slow Waves during Infancy. *Sleep*, *37*(2), 245–253. https://doi.org/10.5665/sleep.3390

Ferguson, K. A., & Cardin, J. A. (2020). Mechanisms underlying gain modulation in the cortex. *Nature Reviews Neuroscience*, *21*(2), 80–92. https://doi.org/10.1038/s41583-019-0253-y

Fernandez, L. M. J., & Lüthi, A. (2020). Sleep Spindles: Mechanisms and Functions. *Physiological Reviews*, *100*(2), 805–868. https://doi.org/10.1152/physrev.00042.2018

Ferrara, M., De Gennaro, L., Casagrande, M., & Bertini, M. (1999). Auditory arousal thresholds after selective slow-wave sleep deprivation. *Clinical Neurophysiology*, *110*(12), 2148–2152. https://doi.org/10.1016/S1388-2457(99)00171-6

Finney, S. J., & DiStefano, C. (2013). Nonnormal and categorical data in structural equation modeling. In *Structural equation modeling: A second course, 2nd ed.* (pp. 439–492). IAP Information Age Publishing.

Fiorillo, L., Puiatti, A., Papandrea, M., Ratti, P.-L., Favaro, P., Roth, C., Bargiotas, P., Bassetti, C. L., & Faraci, F. D. (2019). Automated sleep scoring: A review of the latest approaches. *Sleep Medicine Reviews*, *48*, 101204. https://doi.org/10.1016/j.smrv.2019.07.007

Fletcher, F. E., Knowland, V., Walker, S., Gaskell, M. G., Norbury, C., & Henderson, L. M. (2020). Atypicalities in sleep and semantic consolidation in autism. *Developmental Science*, *23*(3), e12906. https://doi.org/10.1111/desc.12906

Fogel, S. M., & Smith, C. T. (2006). Learning-dependent changes in sleep spindles and Stage 2 sleep. *Journal of Sleep Research*, *15*(3), 250–255. https://doi.org/10.1111/j.1365-2869.2006.00522.x

Forget, D., Morin, C. M., & Bastien, C. H. (2011). The Role of the Spontaneous and Evoked K-Complex in Good-Sleeper Controls and in Individuals with Insomnia. *Sleep*, *34*(9), 1251–1260. https://doi.org/10.5665/SLEEP.1250

Formby, D. (1967). Maternal recognition of infant's cry. *Developmental Medicine & Child Neurology*, *9*(3), 293–298.

Franco, P., Kato, I., Richardson, H. L., Yang, J. S. C., Montemitro, E., & Horne, R. S. C. (2010). Arousal from sleep mechanisms in infants. *Advances in Pediatric Sleep Medicine*, *11*(7), 603–614. https://doi.org/10.1016/j.sleep.2009.12.014

Franco, P., Pardou, A., Hassid, S., Lurquin, P., Groswasser, J., & Kahn, A. (1998). Auditory arousal thresholds are higher when infants sleep in the prone position. *The Journal of Pediatrics*, *132*(2), 240–243. https://doi.org/10.1016/S0022-3476(98)70438-X

Frank, M. G., & Heller, H. C. (2019). The Function(s) of Sleep. In H.-P. Landolt & D.-J. Dijk (Eds.), *Sleep-Wake Neurobiology and Pharmacology* (pp. 3–34). Springer International Publishing. https://doi.org/10.1007/164_2018_140

Frank, M. G., Issa, N. P., & Stryker, M. P. (2001). Sleep Enhances Plasticity in the Developing Visual Cortex. *Neuron*, *30*(1), 275–287. https://doi.org/10.1016/S0896-6273(01)00279-3

Frey, L. C., St Louis, E. K., & Britton, J. W. (2016). *Electroencephalography (EEG): An introductory text and atlas of normal and abnormal findings in adults, children, and infants*. American Epilepsy Society.

Friedrich, M., Wilhelm, I., Born, J., & Friederici, A. D. (2015). Generalization of word meanings during infant sleep. *Nature Communications*, *6*(1), 6004. https://doi.org/10.1038/ncomms7004

Frost-Karlsson, M., Capusan, A. J., Perini, I., Olausson, H., Zetterqvist, M., Gustafsson, P. A., & Boehme, R. (2022). Neural processing of self-touch and other-touch in anorexia nervosa and autism spectrum condition. *NeuroImage: Clinical*, *36*, 103264. https://doi.org/10.1016/j.nicl.2022.103264

Fuerst, D. R., Gallinat, J., & Boutros, N. N. (2007). Range of sensory gating values and test–retest reliability in normal subjects. *Psychophysiology*, *44*(4), 620–626. https://doi.org/10.1111/j.1469-8986.2007.00524.x

Gent, T. C., Bassetti, C. L., & Adamantidis, A. R. (2018). Sleep-wake control and the thalamus. *Systems Neuroscience*, *52*, 188–197. https://doi.org/10.1016/j.conb.2018.08.002

Gibbs, F. A., & Gibbs, E. L. (1950). *Atlas of Electroencephalography: Methodology and Controls.* (2nd ed.). Addison-Wesley Publishing.

Gliga, T., Jones, E. J. H., Bedford, R., Charman, T., & Johnson, M. H. (2014). From early markers to neuro-developmental mechanisms of autism. *Developmental Review : DR*, *34*(3), 189–207. PubMed. https://doi.org/10.1016/j.dr.2014.05.003

Glod, M., Riby, D. M., Honey, E., & Rodgers, J. (2017). Sensory atypicalities in dyads of children with autism spectrum disorder (ASD) and their parents. *Autism Research*, *10*(3), 531–538.

Goff, W. R., Allison, T., Shapiro, A., & Rosner, B. S. (1966). Cerebral somatosensory responses evoked during sleep in man. *Electroencephalography and Clinical Neurophysiology*, *21*(1), 1–9. https://doi.org/10.1016/0013-4694(66)90053-8

Gollob, H. F., & Reichardt, C. S. (1987). Taking Account of Time Lags in Causal Models. *Child Development*, *58*(1), 80–92. JSTOR. https://doi.org/10.2307/1130293

Gong, N. N., Luong, H. N. B., Dang, A. H., Mainwaring, B., Shields, E., Schmeckpeper, K., Bonasio, R., & Kayser, M. S. (2022). Intrinsic maturation of sleep output neurons regulates sleep ontogeny in Drosophila. *Current Biology*, *32*(18), 4025-4039.e3. https://doi.org/10.1016/j.cub.2022.07.054

González, D. A., Wang, D., Pollet, E., Velarde, A., Horn, S., Coss, P., Vaou, O., Wang, J., Li, C., Seshadri, S., Miao, H., & Gonzales, M. M. (2024). Performance of the Dreem 2 EEG headband, relative to polysomnography, for assessing sleep in Parkinson's disease. *Sleep Health: Journal of the National Sleep Foundation*, *10*(1), 24–30. https://doi.org/10.1016/j.sleh.2023.11.012

Goodlin-Jones, B., Burnam, M. M., Gaylor, E. E., & Anders, T. F. (2001). Night Waking, Sleep-Wake Organization, and Self-Soothing in the First Year of Life. *Journal of Developmental & Behavioral Pediatrics*, *22*(4). https://journals.lww.com/jrnldbp/Fulltext/2001/08000/Night_Waking,_Sleep_Wake_Organization,_and.3.aspx

Gorgoni, M., D'Atri, A., Scarpelli, S., Reda, F., & De Gennaro, L. (2020). Sleep electroencephalography and brain maturation: Developmental trajectories and the relation with cognitive functioning. *Sleep Medicine*, *66*, 33–50.

Gossé, L. K., Wiesemann, F., Elwell, C. E., & Jones, E. J. H. (2022). Concordance between subjective and objective measures of infant sleep varies by age and maternal mood: Implications for studies of sleep and cognitive development. *Infant Behavior and Development*, *66*, 101663. https://doi.org/10.1016/j.infbeh.2021.101663

Gottesmann, C. (2002). GABA mechanisms and sleep. *Neuroscience*, *111*(2), 231–239. https://doi.org/10.1016/S0306-4522(02)00034-9

Gramfort, A., Luessi, M., Larson, E., Engemann, D. A., Strohmeier, D., Brodbeck, C., Goj, R., Jas, M., Brooks, T., & Parkkonen, L. (2013). MEG and EEG data analysis with MNE-Python. *Frontiers in Neuroscience*, *7*, 70133.

Grandin, T. (2009). Visual abilities and sensory differences in a person with autism. *Biological Psychiatry*, *65*(1), 15–16.

Grapel, J. N., Cicchetti, D. V., & Volkmar, F. R. (2015). Sensory features as diagnostic criteria for autism: Sensory features in autism. *The Yale Journal of Biology and Medicine*, *88*(1), 69.

Green, L., Willis, E., Ziev, N., Oliveira, D., Kornblau, B., & Robertson, S. (2020). The Impact of Weighted Blankets on the Sleep and Sensory Experiences of Autistic Adults. *AJOT: American Journal of Occupational Therapy*, *74*(S1), NA. Gale Academic OneFile.

Green, S. A., Hernandez, L., Bookheimer, S. Y., & Dapretto, M. (2017). Reduced modulation of thalamocortical connectivity during exposure to sensory stimuli in ASD. *Autism Research*, *10*(5), 801–809.

Griffin, S. C., Ravyts, S. G., Bourchtein, E., Ulmer, C. S., Leggett, M. K., Dzierzewski, J. M., & Calhoun, P. S. (2021). Sleep disturbance and pain in US adults over 50: Evidence for reciprocal, longitudinal effects. *Sleep Medicine*, *86*, 32–39.

Grigg-Damberger Madeleine. (2016). The Visual Scoring of Sleep in Infants 0 to 2 Months of Age. *Journal of Clinical Sleep Medicine*, *12*(03), 429–445. https://doi.org/10.5664/jcsm.5600

Grigg-Damberger Madeleine, Gozal David, Marcus Carole L., Quan Stuart F., Rosen Carol L., Chervin Ronald D., Wise Merrill, Picchietti Daniel L., Sheldon Stephan H., & Iber Conrad. (2007). The Visual Scoring of Sleep and Arousal in Infants and Children. *Journal of Clinical Sleep Medicine*, *03*(02), 201–240. https://doi.org/10.5664/jcsm.26819

Gringras, P., Green, D., Wright, B., Rush, C., Sparrowhawk, M., Pratt, K., Allgar, V., Hooke, N., Moore, D., & Zaiwalla, Z. (2014). Weighted blankets and sleep in autistic children—A randomized controlled trial. *Pediatrics*, *134*(2), 298–306.

Grubb, M. S., & Thompson, I. D. (2004). The influence of early experience on the development of sensory systems. *Current Opinion in Neurobiology*, *14*(4), 503–512. https://doi.org/10.1016/j.conb.2004.06.006

Guang, S., Pang, N., Deng, X., Yang, L., He, F., Wu, L., Chen, C., Yin, F., & Peng, J. (2018). Synaptopathology Involved in Autism Spectrum Disorder. *Frontiers in Cellular Neuroscience*, *12*. https://www.frontiersin.org/journals/cellular-neuroscience/articles/10.3389/fncel.2018.00470

Guillery, R. W., Feig, S. L., & Lozsádi, D. A. (1998). Paying attention to the thalamic reticular nucleus. *Trends in Neurosciences*, *21*(1), 28–32. https://doi.org/10.1016/S0166-2236(97)01157-0

Guiraud, J. A., Kushnerenko, E., Tomalski, P., Davies, K., Ribeiro, H., Johnson, M. H., & The BASIS Team. (2011). Differential habituation to repeated sounds in infants at high risk for autism. *NeuroReport*, *22*(16), 845–849.

Gumenyuk, V., Korzyukov, O., Roth, T., Bowyer, S. M., & Drake, C. L. (2013). Sleep Extension Normalizes ERP of Waking Auditory Sensory Gating in Healthy Habitually Short Sleeping Individuals. *PLOS ONE*, *8*(3), e59007. https://doi.org/10.1371/journal.pone.0059007

Guo, H., Peng, Y., Hu, Z., Li, Y., Xun, G., Ou, J., Sun, L., Xiong, Z., Liu, Y., & Wang, T. (2017). Genome-wide copy number variation analysis in a Chinese autism spectrum disorder cohort. *Scientific Reports*, *7*(1), 44155.

Hairston, I. S., Talbot, L. S., Eidelman, P., Gruber, J., & Harvey, A. G. (2010). Sensory gating in primary insomnia. *European Journal of Neuroscience*, *31*(11), 2112–2121. https://doi.org/10.1111/j.1460-9568.2010.07237.x

Halász, P. (2016). The K-complex as a special reactive sleep slow wave – A theoretical update. *Sleep Medicine Reviews*, *29*, 34–40. https://doi.org/10.1016/j.smrv.2015.09.004

Halasz, P., Kundra, O., Rajna, P., Pal, I., & Vargha, M. (1979). Micro-arousals during nocturnal sleep. *Acta Physiologica Academiae Scientiarum Hungaricae*, *54*(1), 1–12.

Halász, P., Terzano, M., Parrino, L., & Bódizs, R. (2004). The nature of arousal in sleep. *Journal of Sleep Research*, *13*(1), 1–23.

Hamaker, E. L. (2012). Why researchers should think 'within-person': A paradigmatic rationale. In *Handbook of research methods for studying daily life.* (pp. 43–61). The Guilford Press.

Hamaker, E. L. (2018). *How to run the RI-CLPM with Mplus*.

Hamaker, E. L. (2023). The within-between dispute in cross-lagged panel research and how to move forward. *Psychological Methods*, No Pagination Specified-No Pagination Specified. https://doi.org/10.1037/met0000600

Hamaker, E. L., Kuiper, R. M., & Grasman, R. P. P. P. (2015). A critique of the cross-lagged panel model. *Psychological Methods*, *20*(1), 102–116. https://doi.org/10.1037/a0038889

Hamaker, E. L., Mulder, J. D., & van IJzendoorn, M. H. (2020). Description, prediction and causation: Methodological challenges of studying child and adolescent development. *Developmental Cognitive Neuroscience*, *46*, 100867. https://doi.org/10.1016/j.dcn.2020.100867

Hamaker, E. L., & Wichers, M. (2017). No Time Like the Present: Discovering the Hidden Dynamics in Intensive Longitudinal Data. *Current Directions in Psychological Science*, *26*(1), 10–15. https://doi.org/10.1177/0963721416666518

Hansel, C. (2019). Deregulation of synaptic plasticity in autism. *The Cerebellum in Health and Disease*, *688*, 58–61. https://doi.org/10.1016/j.neulet.2018.02.003

Harrington, M. O., & Cairney, S. A. (2021). Sounding It Out: Auditory Stimulation and Overnight Memory Processing. *Current Sleep Medicine Reports*, *7*(3), 112–119. https://doi.org/10.1007/s40675-021-00207-0

Hartman, A. G., McKendry, S., Soehner, A., Bodison, S., Akcakaya, M., DeAlmeida, D., & Bendixen, R. (2022). Characterizing Sleep Differences in Children With and Without Sensory Sensitivities. *Frontiers in Psychology*, *13*, 875766. https://doi.org/10.3389/fpsyg.2022.875766

Haswell, C. C., Izawa, J., Dowell, L. R., Mostofsky, S. H., & Shadmehr, R. (2009). Representation of internal models of action in the autistic brain. *Nature Neuroscience*, *12*(8), 970–972.

Hayat, H., Regev, N., Matosevich, N., Sales, A., Paredes-Rodriguez, E., Krom, A. J., Bergman, L., Li, Y., Lavigne, M., & Kremer, E. J. (2020). Locus coeruleus norepinephrine activity mediates sensory-evoked awakenings from sleep. *Science Advances*, *6*(15), eaaz4232.

Hayes, S. A., & Watson, S. L. (2013). The impact of parenting stress: A meta-analysis of studies comparing the experience of parenting stress in parents of children with and without autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *43*, 629–642.

He, J. L., Williams, Z. J., Harris, A., Powell, H., Schaaf, R., Tavassoli, T., & Puts, N. A. J. (2023). A working taxonomy for describing the sensory differences of autism. *Molecular Autism*, *14*(1), 15. https://doi.org/10.1186/s13229-022-00534-1

Henderson, J. M. T., Blampied, N. M., & France, K. G. (2020). Longitudinal Study of Infant Sleep Development: Early Predictors of Sleep Regulation Across the First Year. *Nature and Science of Sleep*, *12*, 949–957. PubMed. https://doi.org/10.2147/NSS.S240075

Henderson, J. M. T., France, K. G., Owens, J. L., & Blampied, N. M. (2010). Sleeping Through the Night: The Consolidation of Self-regulated Sleep Across the First Year of Life. *Pediatrics*, *126*(5), e1081. https://doi.org/10.1542/peds.2010-0976

Herrera, C. G., & Tarokh, L. (2024). A Thalamocortical Perspective on Sleep Spindle Alterations in Neurodevelopmental Disorders. *Current Sleep Medicine Reports*. https://doi.org/10.1007/s40675-024-00284-x

Hirsh, J., Mar, R., & Peterson, J. (2012). Psychological Entropy: A Framework for Understanding Uncertainty-Related Anxiety. *Psychological Review*, *119*, 304–320. https://doi.org/10.1037/a0026767

Hodge, D., Carollo, T. M., Lewin, M., Hoffman, C. D., & Sweeney, D. P. (2014). Sleep patterns in children with and without autism spectrum disorders: Developmental comparisons. *Research in Developmental Disabilities*, *35*(7), 1631–1638. https://doi.org/10.1016/j.ridd.2014.03.037

Hogeveen, J., Krug, M. K., Geddert, R. M., Ragland, J. D., & Solomon, M. (2020). Compensatory Hippocampal Recruitment Supports Preserved Episodic Memory in Autism Spectrum Disorder. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *5*(1), 97–109. https://doi.org/10.1016/j.bpsc.2019.08.009

Hohn, V. D., de Veld, D. M. J., Mataw, K. J. S., van Someren, E. J. W., & Begeer, S. (2019). Insomnia Severity in Adults with Autism Spectrum Disorder is Associated with sensory Hyper-Reactivity and Social Skill Impairment. *Journal of Autism and Developmental Disorders*, *49*(5), 2146–2155. https://doi.org/10.1007/s10803-019-03891-8

Hollestein, V., Poelmans, G., Forde, N. J., Beckmann, C. F., Ecker, C., Mann, C., Schäfer, T., Moessnang, C., Baumeister, S., Banaschewski, T., Bourgeron, T., Loth, E., Dell'Acqua, F., Murphy, D. G. M., Puts, N. A., Tillmann, J., Charman, T., Jones, E. J. H., Mason, L., … Naaijen, J. (2023). Excitatory/inhibitory imbalance in autism: The role of glutamate and GABA gene-sets in symptoms and cortical brain structure. *Translational Psychiatry*, *13*(1), 18. https://doi.org/10.1038/s41398-023-02317-5

Hollway, J. A., Aman, M. G., & Butter, E. (2013). Correlates and Risk Markers for Sleep Disturbance in Participants of the Autism Treatment Network. *Journal of Autism and Developmental Disorders*, *43*(12), 2830–2843. https://doi.org/10.1007/s10803-013-1830-y

Holz, J., Piosczyk, H., Feige, B., Spiegelhalder, K., Baglioni, C., Riemann, D., & Nissen, C. (2012). EEG sigma and slow-wave activity during NREM sleep correlate with overnight declarative and procedural memory consolidation. *Journal of Sleep Research*, *21*(6), 612–619.

Hu, L., & Bentler, P. M. (1999). Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural Equation Modeling*, *6*(1), 1–55. https://doi.org/10.1080/10705519909540118

Huang, Q., Velthuis, H., Pereira, A. C., Ahmad, J., Cooke, S. F., Ellis, C. L., Ponteduro, F. M., Puts, N. A. J., Dimitrov, M., Batalle, D., Wong, N. M. L., Kowalewski, L., Ivin, G., Daly, E., Murphy, D. G. M., & McAlonan, G. M. (2023). Exploratory evidence for differences in GABAergic regulation of auditory processing in autism spectrum disorder. *Translational Psychiatry*, *13*(1), 320. https://doi.org/10.1038/s41398-023-02619-8

Huber, R., Esser, S. K., Ferrarelli, F., Massimini, M., Peterson, M. J., & Tononi, G. (2007). TMS-induced cortical potentiation during wakefulness locally increases slow wave activity during sleep. *PloS One*, *2*(3), e276.

Humphreys, J. S., Gringras, P., Blair, P. S., Scott, N., Henderson, J., Fleming, P. J., & Emond, A. M. (2014). Sleep patterns in children with autistic spectrum disorders: A prospective cohort

study. *Archives of Disease in Childhood*, *99*(2), 114. https://doi.org/10.1136/archdischild-2013-304083

Hutsler, J. J., & Zhang, H. (2010). Increased dendritic spine densities on cortical projection neurons in autism spectrum disorders. *Brain Research*, *1309*, 83–94. https://doi.org/10.1016/j.brainres.2009.09.120

Hysing, M., Harvey, A. G., Torgersen, L., Ystrom, E., Reichborn-Kjennerud, T., & Sivertsen, B. (2014). Trajectories and predictors of nocturnal awakenings and sleep duration in infants. *Journal of Developmental & Behavioral Pediatrics*, *35*(5), 309–316.

Iber, C., Ancoli-Israel, S., Chesson, A., & Quan, S. (2007). *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications.* American Academy of Sleep Medicine.

Iglowstein, I., Jenni, O. G., Molinari, L., & Largo, R. H. (2003). Sleep duration from infancy to adolescence: Reference values and generational trends. *Pediatrics*, *111*(2), 302–307.

Iotchev, I. B., & Kubinyi, E. (2021). Shared and unique features of mammalian sleep spindles – insights from new and old animal models. *Biological Reviews*, *96*(3), 1021–1034. https://doi.org/10.1111/brv.12688

Irwin, S. A., Patel, B., Idupulapati, M., Harris, J. B., Crisostomo, R. A., Larsen, B. P., Kooy, F., Willems, P. J., Cras, P., & Kozlowski, P. B. (2001). Abnormal dendritic spine characteristics in the temporal and visual cortices of patients with fragile-X syndrome: A quantitative examination. *American Journal of Medical Genetics*, *98*(2), 161–167.

Issa, E. B., & Wang, X. (2011). Altered Neural Responses to Sounds in Primate Primary Auditory Cortex during Slow-Wave Sleep. *The Journal of Neuroscience*, *31*(8), 2965. https://doi.org/10.1523/JNEUROSCI.4920-10.2011

Izawa, J., Pekny, S. E., Marko, M. K., Haswell, C. C., Shadmehr, R., & Mostofsky, S. H. (2012). Motor Learning Relies on Integrated Sensory Inputs in ADHD, but Over-Selectively on Proprioception in Autism Spectrum Conditions. *Autism Research*, *5*(2), 124–136. https://doi.org/10.1002/aur.1222

Jamioł-Milc, D., Bloch, M., Liput, M., Stachowska, L., & Skonieczna-Żydecka, K. (2021). Tactile processing and quality of sleep in autism spectrum disorders. *Brain Sciences*, *11*(3), 362.

Jaramillo, V., Schoch, S. F., Markovic, A., Kohler, M., Huber, R., Lustenberger, C., & Kurth, S. (2023). An infant sleep electroencephalographic marker of thalamocortical connectivity predicts behavioral outcome in late infancy. *NeuroImage*, *269*, 119924. https://doi.org/10.1016/j.neuroimage.2023.119924

Jenni, O. G., Borbély, A. A., & Achermann, P. (2004). Development of the nocturnal sleep electroencephalogram in human infants. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *286*(3), R528–R538. https://doi.org/10.1152/ajpregu.00503.2003

Johnson, L., Hanson, K., & Bickford, R. (1976). Effect of flurazepam on sleep spindles and K-complexes. *Electroencephalography and Clinical Neurophysiology*, *40*(1), 67–77.

Jones, C. E., Chau, A. Q., Olson, R. J., Moore, C., Wickham, P. T., Puranik, N., Guizzetti, M., Cao, H., Meshul, C. K., & Lim, M. M. (2021). Early life sleep disruption alters glutamate and dendritic spines in prefrontal cortex and impairs cognitive flexibility in prairie voles. *Current Research in Neurobiology*, *2*, 100020. https://doi.org/10.1016/j.crneur.2021.100020

Jones, C. E., Opel, R. A., Kaiser, M. E., Chau, A. Q., Quintana, J. R., Nipper, M. A., Finn, D. A., Hammock, E. A. D., & Lim, M. M. (2019). Early-life sleep disruption increases parvalbumin in primary somatosensory cortex and impairs social bonding in prairie voles. *Science Advances*, *5*(1), eaav5188. https://doi.org/10.1126/sciadv.aav5188

Joseph, D., Chong, N. W., Shanks, M. E., Rosato, E., Taub, N. A., Petersen, S. A., Symonds, M. E., Whitehouse, W. P., & Wailoo, M. (2015). Getting rhythm: How do babies do it? *Archives of Disease in Childhood - Fetal and Neonatal Edition*, *100*(1), F50. https://doi.org/10.1136/archdischild-2014-306104

Jouvet-Mounier, D., Astic, L., & Lacote, D. (1969). Ontogenesis of the states of sleep in rat, cat, and guinea pig during the first postnatal month. *Developmental Psychobiology: The Journal of the International Society for Developmental Psychobiology*, *2*(4), 216–239.

Kahn, A., Groswasser, J., Franco, P., Scaillet, S., Sawaguchi, T., Kelmanson, I., & Dan, B. (2003). Sudden infant deaths: Stress, arousal and SIDS. *Early Human Development*, *75*, 147–166. https://doi.org/10.1016/j.earlhumdev.2003.08.018

Kahn, A., Groswasser, J., Rebuffat, E., Sottiaux, M., Blum, D., Foerster, M., Franco, P., Bochner, A., Alexander, M., & Bachy, A. (1992). Sleep and cardiorespiratory characteristics of infant victims of sudden death: A prospective case-control study. *Sleep*, *15*(4), 287–292.

Kamara, D., & Beauchaine, T. P. (2020). A Review of Sleep Disturbances among Infants and Children with Neurodevelopmental Disorders. *Review Journal of Autism and Developmental Disorders*, *7*(3), 278–294. https://doi.org/10.1007/s40489-019-00193-8

Kanner, L. (1943). Autistic disturbances of affective contact. *Nervous Child*, *2*(3), 217–250.

Kärki, A., Satomaa, A.-L., Huhtala, H., Saastamoinen, A., Saarenpää-Heikkilä, O., Paavonen, E. J., & Himanen, S.-L. (2022). Season is related to the slow wave and sigma activity of infants and toddlers. *Sleep Medicine*, *100*, 364–377. https://doi.org/10.1016/j.sleep.2022.09.006

Kattler, H., DIJK, D., & Borbely, A. A. (1994). Effect of unilateral somatosensory stimulation prior to sleep on the sleep EEG in humans. *Journal of Sleep Research*, *3*(3), 159–164.

Kayser, M. S., Yue, Z., & Sehgal, A. (2014). A critical period of sleep for development of courtship circuitry and behavior in Drosophila. *Science*, *344*(6181), 269–274.

Keefe, F. B., Johnson, L. C., & Hunter, E. J. (1971). EEG and autonomic response pattern during waking and sleep stages. *Psychophysiology*, *8*(2), 198–212.

Keith, J. M., Jamieson, J. P., & Bennetto, L. (2019). The Influence of Noise on Autonomic Arousal and Cognitive Performance in Adolescents with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*, *49*(1), 113–126. https://doi.org/10.1007/s10803-018-3685-8

Kercood, S., Grskovic, J. A., Banda, D., & Begeske, J. (2014). Working memory and autism: A review of literature. *Research in Autism Spectrum Disorders*, *8*(10), 1316–1332. https://doi.org/10.1016/j.rasd.2014.06.011

Kim, D., Hwang, E., Lee, M., Sung, H., & Choi, J. H. (2015). Characterization of topographically specific sleep spindles in mice. *Sleep*, *38*(1), 85–96.

Kim, S., Jo, K., Hong, K.-B., Han, S. H., & Suh, H. J. (2019). GABA and l-theanine mixture decreases sleep latency and improves NREM sleep. *Pharmaceutical Biology*, *57*(1), 65–73. PubMed. https://doi.org/10.1080/13880209.2018.1557698

King, E., Campbell, A., Belger, A., & Grewen, K. (2018). Prenatal Nicotine Exposure Disrupts Infant Neural Markers of Orienting. *Nicotine & Tobacco Research*, *20*(7), 897–902. https://doi.org/10.1093/ntr/ntx177

Kisley, M. A., Noecker, T. L., & Guinther, P. M. (2004). Comparison of sensory gating to mismatch negativity and self-reported perceptual phenomena in healthy adults. *Psychophysiology*, *41*(4), 604–612.

Kisley, M. A., Olincy, A., & Freedman, R. (2001). The effect of state on sensory gating: Comparison of waking, REM and non-REM sleep. *Clinical Neurophysiology*, *112*(7), 1154–1165. https://doi.org/10.1016/S1388-2457(01)00578-8

Kılıç, B. K., Kayıhan, H., & Çifci, A. (2024). Sensory processing in typically developing toddlers with and without sleep problems. *Infant Behavior and Development*, *76*, 101981. https://doi.org/10.1016/j.infbeh.2024.101981

Knoblauch, V., Martens, W. L. J., Wirz-Justice, A., & Cajochen, C. (2003). Human sleep spindle characteristics after sleep deprivation. *Clinical Neurophysiology*, *114*(12), 2258–2267. https://doi.org/10.1016/S1388-2457(03)00238-4

Knoop, M. S., de Groot, E. R., & Dudink, J. (2021). Current ideas about the roles of rapid eye movement and non–rapid eye movement sleep in brain development. *Acta Paediatrica*, *110*(1), 36–44. https://doi.org/10.1111/apa.15485

Knowland, V. C. P., Fletcher, F., Henderson, L.-M., Walker, S., Norbury, C. F., & Gaskell, M. G. (2019). Sleep Promotes Phonological Learning in Children Across Language and Autism Spectra. *Journal of Speech, Language, and Hearing Research*, *62*(12), 4235–4255. https://doi.org/10.1044/2019_JSLHR-S-19-0098

Kolenikov, S., & Bollen, K. A. (2012). Testing Negative Error Variances: Is a Heywood Case a Symptom of Misspecification? *Sociological Methods & Research*, *41*(1), 124–167. https://doi.org/10.1177/0049124112442138

Kolesnik, A., Begum Ali, J., Gliga, T., Guiraud, J., Charman, T., Johnson, M., & Jones, E. (2019). Increased cortical reactivity to repeated tones at 8 months in infants with later ASD. *Translational Psychiatry*, *9*(1), 46. https://doi.org/10.1038/s41398-019-0393-x

Krakowiak, P., Goodlin-Jones, B., Hertz-Picciotto, I., Croen, L. A., & Hansen, R. L. (2008). Sleep problems in children with autism spectrum disorders, developmental delays, and typical development: A population-based study. *Journal of Sleep Research*, *17*(2), 197–206. PubMed. https://doi.org/10.1111/j.1365-2869.2008.00650.x

Kramer, M. A., Tort, A. B., & Kopell, N. J. (2008). Sharp edge artifacts and spurious coupling in EEG frequency comodulation measures. *Journal of Neuroscience Methods*, *170*(2), 352–357.

Krause, A. J., Prather, A. A., Wager, T. D., Lindquist, M. A., & Walker, M. P. (2019). The Pain of Sleep Loss: A Brain Characterization in Humans. *The Journal of Neuroscience*, *39*(12), 2291. https://doi.org/10.1523/JNEUROSCI.2408-18.2018

Krol, A., Wimmer, R. D., Halassa, M. M., & Feng, G. (2018). Thalamic Reticular Dysfunction as a Circuit Endophenotype in Neurodevelopmental Disorders. *Neuron*, *98*(2), 282–295. https://doi.org/10.1016/j.neuron.2018.03.021

Kuiper, M. W. M., Verhoeven, E. W. M., & Geurts, H. M. (2019). Stop Making Noise! Auditory Sensitivity in Adults with an Autism Spectrum Disorder Diagnosis: Physiological Habituation and Subjective Detection Thresholds. *Journal of Autism and Developmental Disorders*, *49*(5), 2116–2128. https://doi.org/10.1007/s10803-019-03890-9

Kuiper, R. M., & Ryan, O. (2018). Drawing Conclusions from Cross-Lagged Relationships: Re-Considering the Role of the Time-Interval. *Structural Equation Modeling: A Multidisciplinary Journal*, *25*(5), 809–823. https://doi.org/10.1080/10705511.2018.1431046

Kurdziel, L., Duclos, K., & Spencer, R. M. (2013). Sleep spindles in midday naps enhance learning in preschool children. *Proceedings of the National Academy of Sciences*, *110*(43), 17267–17272.

Kurth, S., Olini, N., Huber, R., & LeBourgeois, M. (2015). Sleep and Early Cortical Development. *Current Sleep Medicine Reports*, *1*(1), 64–73. https://doi.org/10.1007/s40675-014-0002-8

Kurth, S., Ringli, M., Geiger, A., LeBourgeois, M., Jenni, O. G., & Huber, R. (2010). Mapping of cortical activity in the first two decades of life: A high-density sleep electroencephalogram study. *Journal of Neuroscience*, *30*(40), 13211–13219.

Kuznetsova, A., Brockhoff, P. B., & Christensen, R. H. B. (2017). lmerTest Package: Tests in Linear Mixed Effects Models. *Journal of Statistical Software*, *82*(13), 1–26. https://doi.org/10.18637/jss.v082.i13

Kwon, H., Walsh, K. G., Berja, E. D., Manoach, D. S., Eden, U. T., Kramer, M. A., & Chu, C. J. (2023). Sleep spindles in the healthy brain from birth through 18 years. *Sleep*, zsad017. https://doi.org/10.1093/sleep/zsad017

Lambert, A., Tessier, S., Rochette, A.-C., Scherzer, P., Mottron, L., & Godbout, R. (2016). Poor sleep affects daytime functioning in typically developing and autistic children not complaining of sleep problems: A questionnaire-based and polysomnographic study. *Research in Autism Spectrum Disorders*, *23*, 94–106. https://doi.org/10.1016/j.rasd.2015.11.010

Lane, S. J., Leão, M. A., & Spielmann, V. (2022). Sleep, Sensory Integration/Processing, and Autism: A Scoping Review. *Frontiers in Psychology*, *13*. https://www.frontiersin.org/articles/10.3389/fpsyg.2022.877527

Latchoumane, C.-F. V., Ngo, H.-V. V., Born, J., & Shin, H.-S. (2017). Thalamic Spindles Promote Memory Formation during Sleep through Triple Phase-Locking of Cortical, Thalamic, and Hippocampal Rhythms. *Neuron*, *95*(2), 424-435.e6. https://doi.org/10.1016/j.neuron.2017.06.025

Laurino, M., Menicucci, D., Piarulli, A., Mastorci, F., Bedini, R., Allegrini, P., & Gemignani, A. (2014). Disentangling different functional roles of evoked K-complex components: Mapping the sleeping brain while quenching sensory processing. *Neuroimage*, *86*, 433–445.

Lázár, Z. I., Dijk, D.-J., & Lázár, A. S. (2019). Infraslow oscillations in human sleep spindle activity. *Journal of Neuroscience Methods*, *316*, 22–34.

Lecci, S., Cataldi, J., Betta, M., Bernardi, G., Heinzer, R., & Siclari, F. (2020). Electroencephalographic changes associated with subjective under- and overestimation of sleep duration. *Sleep*, *43*(11), zsaa094. https://doi.org/10.1093/sleep/zsaa094

Lecci, S., Fernandez, L. M., Weber, F. D., Cardis, R., Chatton, J.-Y., Born, J., & Lüthi, A. (2017). Coordinated infraslow neural and cardiac oscillations mark fragility and offline periods in mammalian sleep. *Science Advances*, *3*(2), e1602026.

Lechat, B., Hansen, K., Micic, G., Decup, F., Dunbar, C., Liebich, T., Catcheside, P., & Zajamsek, B. (2021). K-complexes are a sensitive marker of noise-related sensory processing during sleep: A pilot study. *Sleep*, *44*(9), zsab065. https://doi.org/10.1093/sleep/zsab065

Lee, E., Lee, J., & Kim, E. (2017). Excitation/Inhibition Imbalance in Animal Models of Autism Spectrum Disorders. *Cortical Excitation-Inhibition Balance and Dysfunction in Psychiatric Disorders*, *81*(10), 838–847. https://doi.org/10.1016/j.biopsych.2016.05.011

Lemieux, M., Chen, J.-Y., Lonjers, P., Bazhenov, M., & Timofeev, I. (2014). The impact of cortical deafferentation on the neocortical slow oscillation. *Journal of Neuroscience*, *34*(16), 5689–5703.

Lendrem, D. (1984). Sleeping and vigilance in birds, II. An experimental study of the Barbary dove (Streptopelia risoria). *Animal Behaviour*, *32*(1), 243–248.

Lenehan, S. M., Fogarty, L., O'Connor, C., Mathieson, S., & Boylan, G. B. (2023). The Architecture of Early Childhood Sleep Over the First Two Years. *Maternal and Child Health Journal*, *27*(2), 226–250. https://doi.org/10.1007/s10995-022-03545-9

Li, W., Ma, L., Yang, G., & Gan, W.-B. (2017). REM sleep selectively prunes and maintains new synapses in development and learning. *Nature Neuroscience*, *20*(3), 427–437. https://doi.org/10.1038/nn.4479

Limoges, É., Bolduc, C., Berthiaume, C., Mottron, L., & Godbout, R. (2013). Relationship between poor sleep and daytime cognitive performance in young adults with autism. *Research in Developmental Disabilities*, *34*(4), 1322–1335. https://doi.org/10.1016/j.ridd.2013.01.013

Linke, A. C., Chen, B., Olson, L., Ibarra, C., Fong, C., Reynolds, S., Apostol, M., Kinnear, M., Müller, R.-A., & Fishman, I. (2021). Sleep Problems in Preschoolers With Autism Spectrum Disorder Are Associated With Sensory Sensitivities and Thalamocortical Overconnectivity. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*. https://doi.org/10.1016/j.bpsc.2021.07.008

Linke, A. C., Jao Keehn, R. J., Pueschel, E. B., Fishman, I., & Müller, R.-A. (2018). Children with ASD show links between aberrant sound processing, social symptoms, and atypical auditory interhemispheric and thalamocortical functional connectivity. *Autism Spectrum Condition – Understanding Sensory and Social Features*, *29*, 117–126. https://doi.org/10.1016/j.dcn.2017.01.007

Little, L. M., Dean, E., Tomchek, S., & Dunn, W. (2018). Sensory Processing Patterns in Autism, Attention Deficit Hyperactivity Disorder, and Typical Development. *Physical & Occupational Therapy In Pediatrics*, *38*(3), 243–254. https://doi.org/10.1080/01942638.2017.1390809

Littlefield, A. K., King, K. M., Acuff, S. F., Foster, K. T., Murphy, J. G., & Witkiewitz, K. (2022). Limitations of cross-lagged panel models in addiction research and alternative models: An empirical example using project MATCH. *Psychology of Addictive Behaviors*, *36*(3), 271–283. https://doi.org/10.1037/adb0000750

Liu, M.-Y., Huang, A., & Huang, N. E. (2017). Evaluating and Improving Automatic Sleep Spindle Detection by Using Multi-Objective Evolutionary Algorithms. *Frontiers in Human Neuroscience*, *11*. https://www.frontiersin.org/journals/human-neuroscience/articles/10.3389/fnhum.2017.00261

Livingstone, M. S., & Hubel, D. H. (1981). Effects of sleep and arousal on the processing of visual information in the cat. *Nature*, *291*(5816), 554–561. https://doi.org/10.1038/291554a0

Lodder, P., Kupper, N., Mols, F., Emons, W. H. M., & Wicherts, J. M. (2022). Assessing the temporal stability of psychological constructs: An illustration of Type D personality, anxiety and depression. *Journal of Research in Personality*, *101*, 104299. https://doi.org/10.1016/j.jrp.2022.104299

Lokhandwala, S., & Spencer, R. M. C. (2022). Relations between sleep patterns early in life and brain development: A review. *Developmental Cognitive Neuroscience*, *56*, 101130. https://doi.org/10.1016/j.dcn.2022.101130

Loomis, A. L., Harvey, E. N., & Hobart, G. (1935a). Further observations on the potential rhythms of the cerebral cortex during sleep. *Science*, *82*, 198–200. https://doi.org/10.1126/science.82.2122.198

Loomis, A. L., Harvey, E. N., & Hobart, G. (1935b). Potential Rhythms of the Cerebral Cortex During Sleep. *Science*, *81*(2111), 597–598. https://doi.org/10.1126/science.81.2111.597

Lord, C. (1999). Autism diagnostic observation schedule. *(No Title)*.

Lord, C., Risi, S., Lambrecht, L., Cook, E. H., Leventhal, B. L., DiLavore, P. C., Pickles, A., & Rutter, M. (2000). The Autism Diagnostic Observation Schedule—Generic: A Standard Measure of Social and Communication Deficits Associated with the Spectrum of Autism. *Journal of Autism and Developmental Disorders*, *30*(3), 205–223. https://doi.org/10.1023/A:1005592401947

Lord, C., Rutter, M., & Le Couteur, A. (1994). Autism Diagnostic Interview-Revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders*, *24*(5), 659–685. https://doi.org/10.1007/BF02172145

Lord, J. S., Gay, S. M., Harper, K. M., Nikolova, V. D., Smith, K. M., Moy, S. S., & Diering, G. H. (2022). Early life sleep disruption potentiates lasting sex-specific changes in behavior in genetically

vulnerable Shank3 heterozygous autism model mice. *Molecular Autism*, *13*(1), 35. https://doi.org/10.1186/s13229-022-00514-5

Lorsung, E., Karthikeyan, R., & Cao, R. (2021). Biological Timing and Neurodevelopmental Disorders: A Role for Circadian Dysfunction in Autism Spectrum Disorders. *Frontiers in Neuroscience*, *15*, 642745–642745. PubMed. https://doi.org/10.3389/fnins.2021.642745

Louis, J., Zhang, J., Revol, M., Debilly, G., & Challamel, M. (1992). Ontogenesis of nocturnal organization of sleep spindles: A longitudinal study during the first 6 months of life. *Electroencephalography and Clinical Neurophysiology*, *83*(5), 289–296.

Luke, S. G. (2017). Evaluating significance in linear mixed-effects models in R. *Behavior Research Methods*, *49*(4), 1494–1502. https://doi.org/10.3758/s13428-016-0809-y

Lupoli, B., Johansson, B., Uvnäs-Moberg, K., & SVENNERSTEN-SJAUNJA, K. (2001). Effect of suckling on the release of oxytocin, prolactin, cortisol, gastrin, cholecystokinin, somatostatin and insulin in dairy cows and their calves. *Journal of Dairy Research*, *68*(2), 175–187.

Lustenberger, C., Boyle, M. R., Alagapan, S., Mellin, J. M., Vaughn, B. V., & Fröhlich, F. (2016). Feedback-Controlled Transcranial Alternating Current Stimulation Reveals a Functional Role of Sleep Spindles in Motor Memory Consolidation. *Current Biology*, *26*(16), 2127–2136. https://doi.org/10.1016/j.cub.2016.06.044

MacDuffie, K. E., Shen, M. D., Dager, S. R., Styner, M. A., Kim, S. H., Paterson, S., Pandey, J., St. John, T., Elison, J. T., Wolff, J. J., Swanson, M. R., Botteron, K. N., Zwaigenbaum, L., Piven, J., & Estes, A. M. (2020). Sleep Onset Problems and Subcortical Development in Infants Later Diagnosed With Autism Spectrum Disorder. *American Journal of Psychiatry*, *177*(6), 518–525. https://doi.org/10.1176/appi.ajp.2019.19060666

Mäkelä, T. E., Kylliäinen, A., Saarenpää-Heikkilä, O., Paavonen, E. J., Paunio, T., Leppänen, J. M., & Peltola, M. J. (2021). Signaled night awakening and its association with social information processing and socio-emotional development across the first two years. *Sleep*, *44*(12), zsab179. https://doi.org/10.1093/sleep/zsab179

Mäkelä, T. E., Peltola, M. J., Nieminen, P., Paavonen, E. J., Saarenpää-Heikkilä, O., Paunio, T., & Kylliäinen, A. (2018). Night awakening in infancy: Developmental stability and longitudinal associations with psychomotor development. *Developmental Psychology*, *54*(7), 1208–1218. https://doi.org/10.1037/dev0000503

Manelis-Baram, L., Meiri, G., Ilan, M., Faroy, M., Michaelovski, A., Flusser, H., Menashe, I., & Dinstein, I. (2021). Sleep Disturbances and Sensory Sensitivities Co-Vary in a Longitudinal Manner in Pre-School Children with Autism Spectrum Disorders. *Journal of Autism and*

Developmental Disorders, 1-15. Advance online publication. https://doi.org/10.1007/s10803-021-04973-2

Maris, E., & Oostenveld, R. (2007). Nonparametric statistical testing of EEG-and MEG-data. *Journal of Neuroscience Methods*, *164*(1), 177–190.

Marshall, L., Helgadóttir, H., Mölle, M., & Born, J. (2006). Boosting slow oscillations during sleep potentiates memory. *Nature*, *444*(7119), 610–613. https://doi.org/10.1038/nature05278

Marshall, P. J., Bar-Haim, Y., & Fox, N. A. (2002). Development of the EEG from 5 months to 4 years of age. *Clinical Neurophysiology*, *113*(8), 1199–1208. https://doi.org/10.1016/S1388-2457(02)00163-3

Martin, S. E., Wraith, P. K., Deary, I. J., & Douglas, N. J. (1997). The effect of nonvisible sleep fragmentation on daytime function. *American Journal of Respiratory and Critical Care Medicine*, *155*(5), 1596–1601. https://doi.org/10.1164/ajrccm.155.5.9154863

Maski, K., Holbrook, H., Manoach, D., Hanson, E., Kapur, K., & Stickgold, R. (2015). Sleep Dependent Memory Consolidation in Children with Autism Spectrum Disorder. *Sleep*, *38*(12), 1955–1963. https://doi.org/10.5665/sleep.5248

Massimini, M., Ferrarelli, F., Huber, R., Esser, S. K., Singh, H., & Tononi, G. (2005). Breakdown of cortical effective connectivity during sleep. *Science*, *309*(5744), 2228–2232.

Massimini, M., Huber, R., Ferrarelli, F., Hill, S., & Tononi, G. (2004). The Sleep Slow Oscillation as a Traveling Wave. *The Journal of Neuroscience*, *24*(31), 6862. https://doi.org/10.1523/JNEUROSCI.1318-04.2004

Matthey, S. (2001). The sleep and settle questionnaire for parents of infants: Psychometric properties. *Journal of Paediatrics and Child Health*, *37*(5), 470–475.

Matthiesen, A., Ransjö-Arvidson, A., Nissen, E., & Uvnäs-Moberg, K. (2001). Postpartum maternal oxytocin release by newborns: Effects of infant hand massage and sucking. *Birth*, *28*(1), 13–19.

Mazurek, M. O., Dovgan, K., Neumeyer, A. M., & Malow, B. A. (2019). Course and Predictors of Sleep and Co-occurring Problems in Children with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*, *49*(5), 2101–2115. https://doi.org/10.1007/s10803-019-03894-5

Mazurek, M. O., & Petroski, G. F. (2015). Sleep problems in children with autism spectrum disorder: Examining the contributions of sensory over-responsivity and anxiety. *Sleep Medicine*, *16*(2), 270–279. https://doi.org/10.1016/j.sleep.2014.11.006

McClain, I. J., Lustenberger, C., Achermann, P., Lassonde, J. M., Kurth, S., & LeBourgeois, M. K. (2016). Developmental Changes in Sleep Spindle Characteristics and Sigma Power across Early Childhood. *Neural Plasticity*, *2016*(1), 3670951. https://doi.org/10.1155/2016/3670951

McCormick, C., Hepburn, S., Young, G. S., & Rogers, S. J. (2016). Sensory symptoms in children with autism spectrum disorder, other developmental disorders and typical development: A longitudinal study. *Autism*, *20*(5), 572–579. https://doi.org/10.1177/1362361315599755

McDiarmid, T. A., Yu, A. J., & Rankin, C. H. (2019). Habituation is more than learning to ignore: Multiple mechanisms serve to facilitate shifts in behavioral strategy. *BioEssays*, *41*(9), 1900077.

McNamara, F., Wulbrand, H., & Thach, B. T. (1998). Characteristics of the infant arousal response. *Journal of Applied Physiology*, *85*(6), 2314–2321. https://doi.org/10.1152/jappl.1998.85.6.2314

McNamara, F., Wulbrand, H., & Thach, B. T. (1999). Habituation of the Infant Arousal Response. *Sleep*, *22*(3), 320–326. https://doi.org/10.1093/sleep/22.3.320

Medina, E., Peterson, S., Ford, K., Singletary, K., & Peixoto, L. (2023). Critical periods and Autism Spectrum Disorders, a role for sleep. *Neurobiology of Sleep and Circadian Rhythms*, *14*, 100088. https://doi.org/10.1016/j.nbscr.2022.100088

Medina, E., Schoch, H., Ford, K., Wintler, T., Singletary, K. G., & Peixoto, L. (2022). Shank3 influences mammalian sleep development. *Journal of Neuroscience Research*, *n/a*(n/a). https://doi.org/10.1002/jnr.25119

Melendres, M. C., Marcus, C. L., Abi-Raad, R. F., Trescher, W. H., Lutz, J. M., & Colrain, I. M. (2008). Respiratory-Related Evoked Potentials During Sleep in Children. *Sleep*, *31*(1), 55–61. https://doi.org/10.1093/sleep/31.1.55

Messinger, D., Young, G. S., Ozonoff, S., Dobkins, K., Carter, A., Zwaigenbaum, L., Landa, R. J., Charman, T., Stone, W. L., Constantino, J. N., Hutman, T., Carver, L. J., Bryson, S., Iverson, J. M., Strauss, M. S., Rogers, S. J., & Sigman, M. (2013). Beyond Autism: A Baby Siblings Research Consortium Study of High-Risk Children at Three Years of Age. *Journal of the American Academy of Child & Adolescent Psychiatry*, *52*(3), 300-308.e1. https://doi.org/10.1016/j.jaac.2012.12.011

Metcalf, D. R., Mondale, J., & Butler, F. K. (1971). Ontogenis of spontaneous K-complexes. *Psychophysiology*, *8*(3), 340–347. https://doi.org/10.1111/j.1469-8986.1971.tb00464.x

Meyer, M., Lamers, D., Kayhan, E., Hunnius, S., & Oostenveld, R. (2021). Enhancing reproducibility in developmental EEG research: BIDS, cluster-based permutation tests, and effect sizes.

Developmental Cognitive Neuroscience, *52*, 101036. https://doi.org/10.1016/j.dcn.2021.101036

Mikkelsen, M., Wodka, E. L., Mostofsky, S. H., & Puts, N. A. J. (2018). Autism spectrum disorder in the scope of tactile processing. *Autism Spectrum Condition – Understanding Sensory and Social Features*, *29*, 140–150. https://doi.org/10.1016/j.dcn.2016.12.005

Milner, C. E., Cuthbert, B. P., Kertesz, R. S., & Cote, K. A. (2009). Sensory gating impairments in poor sleepers during presleep wakefulness. *NeuroReport*, *20*(3), 331–336.

Missig, G., McDougle, C. J., & Carlezon, W. A. (2020). Sleep as a translationally-relevant endpoint in studies of autism spectrum disorder (ASD). *Neuropsychopharmacology*, *45*(1), 90–103. https://doi.org/10.1038/s41386-019-0409-5

Montemitro, E., Franco, P., Scaillet, S., Kato, I., Groswasser, J., Pia Villa, M., Kahn, A., Sastre, J.-P., Ecochard, R., Thiriez, G., & Lin, J.-S. (2008). Maturation of Spontaneous Arousals in Healthy Infants. *Sleep*, *31*(1), 47–54. https://doi.org/10.1093/sleep/31.1.47

Morgan, B. E., Horn, A. R., & Bergman, N. J. (2011). Should neonates sleep alone? *Biological Psychiatry*, *70*(9), 817–825.

Moruzzi, G., & Magoun, H. W. (1949). Brain stem reticular formation and activation of the EEG. *Electroencephalography and Clinical Neurophysiology*, *1*(1), 455–473. https://doi.org/10.1016/0013-4694(49)90219-9

Mühlematter, C., Nielsen, D. S., Castro-Mejía, J. L., Brown, S. A., Rasch, B., Wright, K. P., Jr., Walser, J.-C., Schoch, S. F., & Kurth, S. (2023). Not simply a matter of parents—Infants' sleep-wake patterns are associated with their regularity of eating. *PLOS ONE*, *18*(10), e0291441. https://doi.org/10.1371/journal.pone.0291441

Mukherjee, P., & Kaplan, E. (1995). Dynamics of neurons in the cat lateral geniculate nucleus: In vivo electrophysiology and computational modeling. *Journal of Neurophysiology*, *74*(3), 1222–1243. https://doi.org/10.1152/jn.1995.74.3.1222

Mulder, J. D., & Hamaker, E. L. (2021). Three Extensions of the Random Intercept Cross-Lagged Panel Model. *Structural Equation Modeling: A Multidisciplinary Journal*, *28*(4), 638–648. https://doi.org/10.1080/10705511.2020.1784738

Mullen, E. M. (1995). *Mullen scales of early learning (AGS ed)* (American Guidance Service Inc). American Guidance Service Inc.

Mulligan, S., & White, B. P. (2012). Sensory and Motor Behaviors of Infant Siblings of Children With and Without Autism. *American Journal of Occupational Therapy*, *66*(5), 556–566. https://doi.org/10.5014/ajot.2012.004077

Murata, Y., & Colonnese, M. T. (2019). Thalamic inhibitory circuits and network activity development. *Brain Research*, *1706*, 13–23. https://doi.org/10.1016/j.brainres.2018.10.024

Muthén, L. K., & Muthén, B. O. (1998). *Mplus User's Guide* (Eighth Edition). Muthén & Muthén.

Mylonas, D., Machado, S., Larson, O., Patel, R., Cox, R., Vangel, M., Maski, K., Stickgold, R., & Manoach, D. S. (2022). Dyscoordination of non-rapid eye movement sleep oscillations in autism spectrum disorder. *Sleep*, *45*(3), zsac010. https://doi.org/10.1093/sleep/zsac010

Narmandakh, A., Roest, A. M., Jonge, P. de, & Oldehinkel, A. J. (2020). The bidirectional association between sleep problems and anxiety symptoms in adolescents: A TRAILS report. *Sleep Medicine*, *67*, 39–46. https://doi.org/10.1016/j.sleep.2019.10.018

Neckelmann, D., & Ursin, R. (1993). Sleep stages and EEG power spectrum in relation to acoustical stimulus arousal threshold in the rat. *Sleep*, *16*(5), 467–477.

Ngo, H. V., Claussen, J. C., Born, J., & Mölle, M. (2013). Induction of slow oscillations by rhythmic acoustic stimulation. *Journal of Sleep Research*, *22*(1), 22–31.

Nguyen, A., Murphy, L., Kocak, M., Tylavsky, F., & Pagani, L. (2018). Prospective Associations Between Infant Sleep at 12 Months and Autism Spectrum Disorder Screening Scores at 24 Months in a Community-Based Birth Cohort. *The Journal of Clinical Psychiatry*, *79*(1), 16m11127. https://doi.org/10.4088/JCP.16m11127

Nguyen, J., Zhang, B., Hanson, E., Mylonas, D., & Maski, K. (2022). Neurobehavioral Associations with NREM and REM Sleep Architecture in Children with Autism Spectrum Disorder. *Children*, *9*(9). https://doi.org/10.3390/children9091322

Nicholas, C. L., Trinder, J., & Colrain, I. M. (2002). Increased production of evoked and spontaneous K-complexes following a night of fragmented sleep. *Sleep*, *25*(8), 42–47.

Nordt, M., Hoehl, S., & Weigelt, S. (2016). The use of repetition suppression paradigms in developmental cognitive neuroscience. *Special Issue:Repetition Suppression-an Integrative View*, *80*, 61–75. https://doi.org/10.1016/j.cortex.2016.04.002

Novelli, L., D'atri, A., Marzano, C., Finotti, E., Ferrara, M., Bruni, O., & De Gennaro, L. (2016). Mapping changes in cortical activity during sleep in the first 4 years of life. *Journal of Sleep Research*, *25*(4), 381–389.

O'Donovan, M. J., & Rinzel, J. (1997). Synaptic depression: A dynamic regulator of synaptic communication with varied functional roles. *Trends in Neurosciences*, *20*(10), 431–433.

Ohlsson, B., Forsling, M. L., Rehfeld, J. F., & Sjölund, K. (2002). Cholecystokinin stimulation leads to increased oxytocin secretion in women. *The European Journal of Surgery*, *168*(2), 114–118.

Oishi, Y., Saito, Y. C., & Sakurai, T. (2023). GABAergic modulation of sleep-wake states. *Pharmacology & Therapeutics*, *249*, 108505. https://doi.org/10.1016/j.pharmthera.2023.108505

Okumura, T., Kumazaki, H., Singh, A. K., Touhara, K., & Okamoto, M. (2019). Individuals With Autism Spectrum Disorder Show Altered Event-Related Potentials in the Late Stages of Olfactory Processing. *Chemical Senses*, *bjz070*. https://doi.org/10.1093/chemse/bjz070

Öngür, D., & Price, J. L. (2000). The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cerebral Cortex*, *10*(3), 206–219. Scopus. https://doi.org/10.1093/cercor/10.3.206

O'Reilly, C., Huberty, S., van Noordt, S., Desjardins, J., Wright, N., Scorah, J., Webb, S. J., Elsabbagh, M., Baron-Cohen, S., Bolton, P., Chandler, S., Charman, T., Fernandes, J., Garwood, H., Hudryx, K., Johnson, M. H., Tucker, L., Volein, A., & BASIS team. (2023). EEG functional connectivity in infants at elevated familial likelihood for autism spectrum disorder. *Molecular Autism*, *14*(1), 37. https://doi.org/10.1186/s13229-023-00570-5

Orekhova, E. V., Stroganova, T. A., Nygren, G., Tsetlin, M. M., Posikera, I. N., Gillberg, C., & Elam, M. (2007). Excess of High Frequency Electroencephalogram Oscillations in Boys with Autism. *Autism and Attention Deficit Hyperactivity Disorder*, *62*(9), 1022–1029. https://doi.org/10.1016/j.biopsych.2006.12.029

Oswald, I., Taylor, A. M., & Treisman, M. (1960). Discriminative responses to stimulation during human sleep. *Brain: A Journal of Neurology*, *83*, 440–453. https://doi.org/10.1093/brain/83.3.440

Owens, J., Spirito, A., & McGuinn, M. (2000). *The Children's Sleep Habits Questionnaire (CSHQ): Psychometric properties of a survey instrument for school-aged children. Sleep: Journal of Sleep Research & Sleep Medicine, 23 (8), 1–9*.

Ozonoff, S., Young, G. S., Bradshaw, J., Charman, T., Chawarska, K., Iverson, J. M., Klaiman, C., Landa, R. J., McDonald, N., Messinger, D., Schmidt, R. J., Wilkinson, C. L., & Zwaigenbaum, L. (2024). Familial Recurrence of Autism: Updates From the Baby Siblings Research Consortium. *Pediatrics*, *154*(2), e2023065297. https://doi.org/10.1542/peds.2023-065297

Ozonoff, S., Young, G. S., Carter, A., Messinger, D., Yirmiya, N., Zwaigenbaum, L., Bryson, S., Carver, L. J., Constantino, J. N., Dobkins, K., Hutman, T., Iverson, J. M., Landa, R., Rogers, S. J., Sigman, M., & Stone, W. L. (2011). Recurrence risk for autism spectrum disorders: A Baby Siblings Research Consortium study. *Pediatrics*, *128*(3), e488–e495. PubMed. https://doi.org/10.1542/peds.2010-2825

Öztürk-Çolak, A., Inami, S., Buchler, J. R., McClanahan, P. D., Cruz, A., Fang-Yen, C., & Koh, K. (2020). Sleep induction by mechanosensory stimulation in Drosophila. *Cell Reports*, *33*(9).

Page, J. (2018). *Characterizing Early Development and NREM Sleep In Infants and Toddles and Risk for Autism Disorder*. https://doi.org/10.17615/8m09-6n17

Page, J., Lustenberger, C., & Fröhlich, F. (2020). Nonrapid eye movement sleep and risk for autism spectrum disorder in early development: A topographical electroencephalogram pilot study. *Brain and Behavior*, *10*(3), e01557. https://doi.org/10.1002/brb3.1557

Pappenheimer, J., Koski, G., Fencl, V., Karnovsky, M., & Krueger, J. (1975). Extraction of sleep-promoting factor S from cerebrospinal fluid and from brains of sleep-deprived animals. *Journal of Neurophysiology*, *38*(6), 1299–1311.

Parapatics, S., Anderer, P., Gruber, G., Saletu, B., Saletu-Zyhlarz, G., & Dorffner, G. (2015). K-complex amplitude as a marker of sleep homeostasis in obstructive sleep apnea syndrome and healthy controls. *Somnologie - Schlafforschung Und Schlafmedizin*, *19*(1), 22–29. https://doi.org/10.1007/s11818-015-0701-5

Parise, E., & Csibra, G. (2013). Neural responses to multimodal ostensive signals in 5-month-old infants. *PloS One*, *8*(8), e72360–e72360. PubMed. https://doi.org/10.1371/journal.pone.0072360

Park, I., Díaz, J., Matsumoto, S., Iwayama, K., Nabekura, Y., Ogata, H., Kayaba, M., Aoyagi, A., Yajima, K., Satoh, M., Tokuyama, K., & Vogt, K. E. (2021). Exercise improves the quality of slow-wave sleep by increasing slow-wave stability. *Scientific Reports*, *11*(1), 4410. https://doi.org/10.1038/s41598-021-83817-6

Paus, T., Collins, D., Evans, A., Leonard, G., Pike, B., & Zijdenbos, A. (2001). Maturation of white matter in the human brain: A review of magnetic resonance studies. *Brain Research Bulletin*, *54*(3), 255–266.

Peerboom, C., & Wierenga, C. J. (2021). The postnatal GABA shift: A developmental perspective. *Neuroscience & Biobehavioral Reviews*, *124*, 179–192. https://doi.org/10.1016/j.neubiorev.2021.01.024

Petruzzelli, M. G., Matera, E., Giambersio, D., Marzulli, L., Gabellone, A., Legrottaglie, A. R., Margari, A., & Margari, L. (2021). Subjective and Electroencephalographic Sleep Parameters in Children and Adolescents with Autism Spectrum Disorder: A Systematic Review. *Journal of Clinical Medicine*, *10*(17). https://doi.org/10.3390/jcm10173893

Peyrache, A., & Seibt, J. (2020). A mechanism for learning with sleep spindles. *Philosophical Transactions of the Royal Society B*, *375*(1799), 20190230.

Piccardi, E. S., Begum Ali, J., Jones, E. J. H., Mason, L., Charman, T., Johnson, M. H., Gliga, T., Agyapong, M., Bazelmans, T., Dafner, L., Ersoy, M., Goodwin, A., Haartsen, R., Hendry, A., Holman, R., Kalwarowsky, S., Kolesnik, A., Lloyd-Fox, S., Pasco, G., … BASIS/STAARS Team. (2021). Behavioural and neural markers of tactile sensory processing in infants at elevated likelihood of autism spectrum disorder and/or attention deficit hyperactivity disorder.

Journal of Neurodevelopmental Disorders, *13*(1), 1. https://doi.org/10.1186/s11689-020-09334-1

Pinault, D. (2004). The thalamic reticular nucleus: Structure, function and concept. *Brain Research Reviews*, *46*(1), 1–31. https://doi.org/10.1016/j.brainresrev.2004.04.008

Pirchio, M., Turner, J., Williams, S., Asprodini, E., & Crunelli, V. (1997). Postnatal development of membrane properties and δ oscillations in thalamocortical neurons of the cat dorsal lateral geniculate nucleus. *Journal of Neuroscience*, *17*(14), 5428–5444.

Pisch, M. (2015). *A longitudinal study of infant sleep and its effects on cognitive development*.

Pittner, K., Rasmussen, J., Lim, M. M., Gilmore, J. H., Styner, M., Entringer, S., Wadhwa, P. D., & Buss, C. (2023). Sleep across the first year of life is prospectively associated with brain volume in 12-months old infants. *Neurobiology of Sleep and Circadian Rhythms*, *14*, 100091. https://doi.org/10.1016/j.nbscr.2023.100091

Poe, A. R., Zhu, L., Szuperak, M., McClanahan, P. D., Anafi, R. C., Scholl, B., Thum, A. S., Cavanaugh, D. J., & Kayser, M. S. (2023). Developmental emergence of sleep rhythms enables long-term memory in Drosophila. *Science Advances*, *9*(36), eadh2301. https://doi.org/10.1126/sciadv.adh2301

Portas, C. M., Krakow, K., Allen, P., Josephs, O., Armony, J. L., & Frith, C. D. (2000). Auditory processing across the sleep-wake cycle: Simultaneous EEG and fMRI monitoring in humans. *Neuron*, *28*(3), 991–999.

Prehn-Kristensen, A., Göder, R., Fischer, J., Wilhelm, I., Seeck-Hirschner, M., Aldenhoff, J., & Baving, L. (2011). Reduced sleep-associated consolidation of declarative memory in attention-deficit/hyperactivity disorder. *Sleep Medicine*, *12*(7), 672–679.

Priddis, L. E. (2009). Tuned in parenting and infant sleep patterns. *Early Child Development and Care*, *179*(3), 259–269. https://doi.org/10.1080/03004430600912132

Pugin, F., Metz, A. J., Wolf, M., Achermann, P., Jenni, O. G., & Huber, R. (2015). Local increase of sleep slow wave activity after three weeks of working memory training in children and adolescents. *Sleep*, *38*(4), 607–614.

Purcell, S. M., Manoach, D. S., Demanuele, C., Cade, B. E., Mariani, S., Cox, R., Panagiotaropoulou, G., Saxena, R., Pan, J. Q., Smoller, J. W., Redline, S., & Stickgold, R. (2017). Characterizing sleep spindles in 11,630 individuals from the National Sleep Research Resource. *Nature Communications*, *8*(1), 15930. https://doi.org/10.1038/ncomms15930

Putnam, S. P., Helbig, A. L., Gartstein, M. A., Rothbart, M. K., & Leerkes, E. (2014). Development and assessment of short and very short forms of the Infant Behavior Questionnaire–Revised. *Journal of Personality Assessment*, *96*(4), 445–458.

Puts, N. A. J., Wodka, E. L., Harris, A. D., Crocetti, D., Tommerdahl, M., Mostofsky, S. H., & Edden, R. A. E. (2017). Reduced GABA and altered somatosensory function in children with autism spectrum disorder. *Autism Research*, *10*(4), 608–619. https://doi.org/10.1002/aur.1691

Rajna, P., Halász, P., Kundra, O., & Pál, I. (1983). Event-related non-specific responses (K-complexes) during sleep. *Acta Medica Hungarica*, *40*(1), 33–40.

Rakic, P., Bourgeois, J.-P., Eckenhoff, M. F., Zecevic, N., & Goldman-Rakic, P. S. (1986). Concurrent overproduction of synapses in diverse regions of the primate cerebral cortex. *Science*, *232*(4747), 232–235.

Ranjan, R., Arya, R., Fernandes, S. L., Sravya, E., & Jain, V. (2018). A fuzzy neural network approach for automatic K-complex detection in sleep EEG signal. *Multimodal Fusion for Pattern Recognition*, *115*, 74–83. https://doi.org/10.1016/j.patrec.2018.01.001

Rantamäki, T., & Kohtala, S. (2020). Encoding, Consolidation, and Renormalization in Depression: Synaptic Homeostasis, Plasticity, and Sleep Integrate Rapid Antidepressant Effects. *Pharmacological Reviews*, *72*, 439–465. https://doi.org/10.1124/pr.119.018697

Rasch, B., & Born, J. (2013). About sleep's role in memory. *Physiological Reviews*, *93*(2), 681–766. PubMed. https://doi.org/10.1152/physrev.00032.2012

Rebuffat, E., Groswasser, J., Kelmanson, I., Sottiaux, M., & Kahn, A. (1994). Polygraphic evaluation of night-to-night variability in sleep characteristics and apneas in infants. *Sleep*, *17*(4), 329–332.

Rechtschaffen, A. (1998). Current perspectives on the function of sleep. *Perspectives in Biology and Medicine*, *41*(3), 359–390.

Reynolds, S., Lane, S. J., & Thacker, L. (2012). Sensory Processing, Physiological Stress, and Sleep Behaviors in Children with and without Autism Spectrum Disorders. *OTJR: Occupational Therapy Journal of Research*, *32*(1), 246–257. https://doi.org/10.3928/15394492-20110513-02

Richdale, A. L., Baker, E., Short, M., & Gradisar, M. (2014). The role of insomnia, pre-sleep arousal and psychopathology symptoms in daytime impairment in adolescents with high-functioning autism spectrum disorder. *Sleep Medicine*, *15*(9), 1082–1088. https://doi.org/10.1016/j.sleep.2014.05.005

Riedner, B. A., Hulse, B. K., Murphy, M. J., Ferrarelli, F., & Tononi, G. (2011). Temporal dynamics of cortical sources underlying spontaneous and peripherally evoked slow waves. *Progress in Brain Research*, *193*, 201–218.

Riemann, D., Spiegelhalder, K., Feige, B., Voderholzer, U., Berger, M., Perlis, M., & Nissen, C. (2010). The hyperarousal model of insomnia: A review of the concept and its evidence. *Sleep Medicine Reviews*, *14*(1), 19–31. https://doi.org/10.1016/j.smrv.2009.04.002

Riggins, T., Ratliff, E. L., Horger, M. N., & Spencer, R. M. C. (2024). The importance of sleep for the developing brain. *Current Sleep Medicine Reports*. https://doi.org/10.1007/s40675-024-00307-7

Riggins, T., & Spencer, R. M. (2020). Habitual sleep is associated with both source memory and hippocampal subfield volume during early childhood. *Scientific Reports*, *10*(1), 15304.

Ringli, M., & Huber, R. (2011). Chapter 5—Developmental aspects of sleep slow waves: Linking sleep, brain maturation and behavior. In E. J. W. Van Someren, Y. D. Van Der Werf, P. R. Roelfsema, H. D. Mansvelder, & F. H. Lopes Da Silva (Eds.), *Progress in Brain Research* (Vol. 193, pp. 63–82). Elsevier. https://doi.org/10.1016/B978-0-444-53839-0.00005-3

Robertson, A. E., & Simmons, D. R. (2013). The relationship between sensory sensitivity and autistic traits in the general population. *Journal of Autism and Developmental Disorders*, *43*, 775–784.

Rodriguez, A. V., Funk, C. M., Vyazovskiy, V. V., Nir, Y., Tononi, G., & Cirelli, C. (2016). Why Does Sleep Slow-Wave Activity Increase After Extended Wake? Assessing the Effects of Increased Cortical Firing During Wake and Sleep. *The Journal of Neuroscience*, *36*(49), 12436. https://doi.org/10.1523/JNEUROSCI.1614-16.2016

Roffwarg, H. P., Muzio, J. N., & Dement, W. C. (1966). Ontogenetic Development of the Human Sleep-Dream Cycle: The prime role of" dreaming sleep" in early life may be in the development of the central nervous system. *Science*, *152*(3722), 604–619.

Rogosa, D. (1980). A critique of cross-lagged correlation. *Psychological Bulletin*, *88*(2), 245–258. https://doi.org/10.1037/0033-2909.88.2.245

Rosanova, M., & Timofeev, I. (2005). Neuronal mechanisms mediating the variability of somatosensory evoked potentials during sleep oscillations in cats. *The Journal of Physiology*, *562*(2), 569–582.

Ruby, P., Caclin, A., Boulet, S., Delpuech, C., & Morlet, D. (2008). Odd sound processing in the sleeping brain. *Journal of Cognitive Neuroscience*, *20*(2), 296–311.

Rudzik, F., Thiesse, L., Pieren, R., Wunderli, J. M., Brink, M., Foraster, M., Héritier, H., Eze, I. C., Garbazza, C., Vienneau, D., Probst-Hensch, N., Röösli, M., & Cajochen, C. (2018). Sleep spindle characteristics and arousability from nighttime transportation noise exposure in healthy young and older individuals. *Sleep*, *41*(7), zsy077. https://doi.org/10.1093/sleep/zsy077

Sacrey, L.-A. R., Zwaigenbaum, L., Bryson, S., Brian, J., Smith, I. M., Roberts, W., Szatmari, P., Roncadin, C., Garon, N., & Novak, C. (2015). Can parents' concerns predict autism spectrum

disorder? A prospective study of high-risk siblings from 6 to 36 months of age. *Journal of the American Academy of Child & Adolescent Psychiatry*, *54*(6), 470–478.

Sadeh, A. (1996). Evaluating Night Wakings in Sleep-Disturbed Infants: A Methodological Study of Parental Reports and Actigraphy. *Sleep*, *19*(10), 757–762. https://doi.org/10.1093/sleep/19.10.757

Sanchez-Vives, M. V., & McCormick, D. A. (2000). Cellular and network mechanisms of rhythmic recurrent activity in neocortex. *Nature Neuroscience*, *3*(10), 1027–1034.

Sassenhagen, J., & Draschkow, D. (2019). Cluster-based permutation tests of MEG/EEG data do not establish significance of effect latency or location. *Psychophysiology*, *56*(6), e13335. https://doi.org/10.1111/psyp.13335

Sato, Y., Fukuoka, Y., Minamitani, H., & Honda, K. (2007). Sensory stimulation triggers spindles during sleep stage 2. *Sleep*, *30*(4), 511–518.

Satomaa, A.-L., Mäkelä, T., Saarenpää-Heikkilä, O., Kylliäinen, A., Huupponen, E., & Himanen, S.-L. (2020). Slow-wave activity and sigma activities are associated with psychomotor development at 8 months of age. *Sleep*, *43*(9), zsaa061.

Satorra, A., & Saris, W. E. (1985). Power of the likelihood ratio test in covariance structure analysis. *Psychometrika*, *50*(1), 83–90. https://doi.org/10.1007/BF02294150

Schabus, M., Dang-Vu, T. T., Heib, D., Boly, M., Desseilles, M., Vandewalle, G., Schmidt, C., Albouy, G., Darsaud, A., Gais, S., Degueldre, C., Balteau, E., Phillips, C., Luxen, A., & Maquet, P. (2012). The Fate of Incoming Stimuli during NREM Sleep is Determined by Spindles and the Phase of the Slow Oscillation. *Frontiers in Neurology*, *3*. https://www.frontiersin.org/articles/10.3389/fneur.2012.00040

Schabus, M., Gruber, G., Parapatics, S., Sauter, C., Klösch, G., Anderer, P., Klimesch, W., Saletu, B., & Zeitlhofer, J. (2004). Sleep Spindles and Their Significance for Declarative Memory Consolidation. *Sleep*, *27*(8), 1479–1485. https://doi.org/10.1093/sleep/27.7.1479

Schechtman, V. L., Harper, R. M., Wilson, A. J., & Southall, D. P. (1992). Sleep state organization in normal infants and victims of the sudden infant death syndrome. *Pediatrics*, *89*(5), 865–870.

Schieber, J. P., Muzet, A., & Ferriere, P. J. (1971). Les phases d'activation transitoire spontanées au cours du sommeil normal chez l'homme. *Archives Des Sciences Physiologiques*, *25*(4), 443:65.

Schielzeth, H., Dingemanse, N. J., Nakagawa, S., Westneat, D. F., Allegue, H., Teplitsky, C., Réale, D., Dochtermann, N. A., Garamszegi, L. Z., & Araya-Ajoy, Y. G. (2020). Robustness of linear mixed-effects models to violations of distributional assumptions. *Methods in Ecology and Evolution*, *11*(9), 1141–1152. https://doi.org/10.1111/2041-210X.13434

Schneider, J., Lewis, P. A., Koester, D., Born, J., & Ngo, H.-V. V. (2020). Susceptibility to auditory closed-loop stimulation of sleep slow oscillations changes with age. *Sleep*, *43*(12), zsaa111. https://doi.org/10.1093/sleep/zsaa111

Schneider, W. T., Vas, S., Nicol, A. U., & Morton, A. J. (2020). Characterizing sleep spindles in sheep. *Eneuro*, *7*(2).

Schoch, S. F., Kurth, S., & Werner, H. (2021). Actigraphy in sleep research with infants and young children: Current practices and future benefits of standardized reporting. *Journal of Sleep Research*, *30*(3), e13134. https://doi.org/10.1111/jsr.13134

Scholle, S., Zwacka, G., & Scholle, H. C. (2007). Sleep spindle evolution from infancy to adolescence. *Clinical Neurophysiology*, *118*(7), 1525–1531. https://doi.org/10.1016/j.clinph.2007.03.007

Sela, Y., Vyazovskiy, V. V., Cirelli, C., Tononi, G., & Nir, Y. (2016). Responses in Rat Core Auditory Cortex are Preserved during Sleep Spindle Oscillations. *Sleep*, *39*(5), 1069–1082. https://doi.org/10.5665/sleep.5758

Sengupta, P. (2013). The laboratory rat: Relating its age with human's. *International Journal of Preventive Medicine*, *4*(6), 624.

Sharon, O., & Nir, Y. (2018). Attenuated Fast Steady-State Visual Evoked Potentials During Human Sleep. *Cerebral Cortex*, *28*(4), 1297–1311. https://doi.org/10.1093/cercor/bhx043

Shaw, P., Kabani, N. J., Lerch, J. P., Eckstrand, K., Lenroot, R., Gogtay, N., Greenstein, D., Clasen, L., Evans, A., & Rapoport, J. L. (2008). Neurodevelopmental trajectories of the human cerebral cortex. *Journal of Neuroscience*, *28*(14), 3586–3594.

Shi, Q., Butner, J. E., Kilshaw, R., Munion, A., Deboeck, P., Oh, Y., & Berg, C. A. (2023). A comparison of models for inferring longitudinal reciprocal relationships between constructs: A case example with internalizing and externalizing problems. *Social Development*, *32*(1), 47–72. https://doi.org/10.1111/sode.12628

Siclari, F., & Tononi, G. (2017). Local aspects of sleep and wakefulness. *Current Opinion in Neurobiology*, *44*, 222–227.

Sidor, A., Fischer, C., Eickhorst, A., & Cierpka, M. (2013). Influence of early regulatory problems in infants on their development at 12 months: A longitudinal study in a high-risk sample. *Child and Adolescent Psychiatry and Mental Health*, *7*(1), 35. https://doi.org/10.1186/1753-2000-7-35

Silva, L. M. T., Cignolini, A., Warren, R., Budden, S., & Skowron-Gooch, A. (2007). Improvement in Sensory Impairment and Social Interaction in Young Children with Autism Following Treatment with an Original Qigong Massage Methodology. *The American Journal of Chinese Medicine*, *35*(03), 393–406. https://doi.org/10.1142/S0192415X07004916

Simmons, D. R., Robertson, A. E., McKay, L. S., Toal, E., McAleer, P., & Pollick, F. E. (2009). Vision in autism spectrum disorders. *Vision Research*, *49*(22), 2705–2739.

Simon, K. N. S., Werchan, D., Goldstein, M. R., Sweeney, L., Bootzin, R. R., Nadel, L., & Gómez, R. L. (2017). Sleep confers a benefit for retention of statistical language learning in 6.5month old infants. *Sleep and Language Learning*, *167*, 3–12. https://doi.org/10.1016/j.bandl.2016.05.002

Sinai, D., & Tikotzky, L. (2012). Infant sleep, parental sleep and parenting stress in families of mothers on maternity leave and in families of working mothers. *Infant Behavior and Development*, *35*(2), 179–186. https://doi.org/10.1016/j.infbeh.2012.01.006

Siper, P. M., Kolevzon, A., Wang, A. T., Buxbaum, J. D., & Tavassoli, T. (2017). A clinician-administered observation and corresponding caregiver interview capturing DSM-5 sensory reactivity symptoms in children with ASD. *Autism Research*, *10*(6), 1133–1140.

Skeldon, A. C., Derks, G., & Dijk, D.-J. (2016). Modelling changes in sleep timing and duration across the lifespan: Changes in circadian rhythmicity or sleep homeostasis? *Sleep Medicine Reviews*, *28*, 96–107. https://doi.org/10.1016/j.smrv.2015.05.011

Smith, F. R., Gaskell, M. G., Weighall, A. R., Warmington, M., Reid, A. M., & Henderson, L. M. (2018). Consolidation of vocabulary is associated with sleep in typically developing children, but not in children with dyslexia. *Developmental Science*, *21*(5), e12639.

Sokoloff, G., Dooley, J. C., Glanz, R. M., Wen, R. Y., Hickerson, M. M., Evans, L. G., Laughlin, H. M., Apfelbaum, K. S., & Blumberg, M. S. (2021). Twitches emerge postnatally during quiet sleep in human infants and are synchronized with sleep spindles. *Current Biology*, *31*(15), 3426-3432.e4. https://doi.org/10.1016/j.cub.2021.05.038

Solomon, S., Dinstein, I., Menashe, I., & Meiri, G. (2022). Children with autism and insomnia utilize twice the amount of health services than their counterparts. *Abstracts from the 16th World Sleep Congress, March 11-16, 2022 in Rome, Italy*, *100*, S212. https://doi.org/10.1016/j.sleep.2022.05.571

Sommer, M. A., & Wurtz, R. H. (2002). A pathway in primate brain for internal monitoring of movements. *Science*, *296*(5572), 1480–1482.

Sorondo, B. M., & Reeb-Sutherland, B. C. (2015). Associations between infant temperament, maternal stress, and infants' sleep across the first year of life. *Infant Behavior and Development*, *39*, 131–135. https://doi.org/10.1016/j.infbeh.2015.02.010

Souders, M. C., Zavodny, S., Eriksen, W., Sinko, R., Connell, J., Kerns, C., Schaaf, R., & Pinto-Martin, J. (2017). Sleep in Children with Autism Spectrum Disorder. *Current Psychiatry Reports*, *19*(6), 34. https://doi.org/10.1007/s11920-017-0782-x

Sparrow, S. S., & Cicchetti, D. V. (1989). The Vineland Adaptive Behavior Scales. In *Major psychological assessment instruments, Vol. 2.* (pp. 199–231). Allyn & Bacon.

Spencer, R. M., & Riggins, T. (2022). Contributions of memory and brain development to the bioregulation of naps and nap transitions in early childhood. *Proceedings of the National Academy of Sciences*, *119*(44), e2123415119.

Spira, G. (2021). A sensory intervention to improve sleep behaviors and sensory processing behaviors of children with sensory processing disorders. *Irish Journal of Occupational Therapy*, *49*(1). https://doi.org/10.1108/IJOT-09-2020-0014

Squires, J., & Bricker, D. (2009). Ages & Stages Questionnaires®, Third Edition (ASQ®-3): A Parent-Completed Child Monitoring System. *Paul H. Brookes Publishing Co., Inc.*

Staton, S., Rankin, P. S., Harding, M., Smith, S. S., Westwood, E., LeBourgeois, M. K., & Thorpe, K. J. (2020). Many naps, one nap, none: A systematic review and meta-analysis of napping patterns in children 0–12 years. *Sleep Medicine Reviews*, *50*, 101247.

Steiner, A. M., Goldsmith, T. R., Snow, A. V., & Chawarska, K. (2012). Practitioner's guide to assessment of autism spectrum disorders in infants and toddlers. *Journal of Autism and Developmental Disorders*, *42*(6), 1183–1196. PubMed. https://doi.org/10.1007/s10803-011-1376-9

Stepanski, E. J. (2002). The effect of sleep fragmentation on daytime function. *Sleep*, *25*(3), 268–276.

Steriade, M., Deschenes, M., Domich, L., & Mulle, C. (1985). Abolition of spindle oscillations in thalamic neurons disconnected from nucleus reticularis thalami. *Journal of Neurophysiology*, *54*(6), 1473–1497. https://doi.org/10.1152/jn.1985.54.6.1473

Steriade, M., Nunez, A., & Amzica, F. (1993). A novel slow (< 1 Hz) oscillation of neocortical neurons in vivo: Depolarizing and hyperpolarizing components. *Journal of Neuroscience*, *13*(8), 3252–3265.

Strauss, M., & Dehaene, S. (2019). Detection of arithmetic violations during sleep. *Sleep*, *42*(3), zsy232.

Tamaki, M., Bang, J. W., Watanabe, T., & Sasaki, Y. (2016). Night watch in one brain hemisphere during sleep associated with the first-night effect in humans. *Current Biology*, *26*(9), 1190–1194.

Tapia-Rivas, N. I., Estévez, P. A., & Cortes-Briones, J. A. (2024). A robust deep learning detector for sleep spindles and K-complexes: Towards population norms. *Scientific Reports*, *14*(1), 263. https://doi.org/10.1038/s41598-023-50736-7

Tavassoli, T., & Baron-Cohen, S. (2012a). Olfactory detection thresholds and adaptation in adults with autism spectrum condition. *Journal of Autism and Developmental Disorders*, *42*, 905–909.

Tavassoli, T., & Baron-Cohen, S. (2012b). Taste identification in adults with autism spectrum conditions. *Journal of Autism and Developmental Disorders*, *42*, 1419–1424.

Tavassoli, T., Miller, L. J., Schoen, S. A., Nielsen, D. M., & Baron-Cohen, S. (2014). Sensory over-responsivity in adults with autism spectrum conditions. *Autism*, *18*(4), 428–432.

The International Paediatric Work Group On Arousals. (2005). The scoring of arousals in healthy term infants (between the ages of 1 and 6 months). *Journal of Sleep Research*, *14*(1), 37–41. https://doi.org/10.1111/j.1365-2869.2004.00426.x

Timofeev, I., Schoch, S. F., LeBourgeois, M. K., Huber, R., Riedner, B. A., & Kurth, S. (2020). Spatio-temporal properties of sleep slow waves and implications for development. *Physiology of Sleep*, *15*, 172–182. https://doi.org/10.1016/j.cophys.2020.01.007

Timofeev, I., & Steriade, M. (1996). Low-frequency rhythms in the thalamus of intact-cortex and decorticated cats. *Journal of Neurophysiology*, *76*(6), 4152–4168. https://doi.org/10.1152/jn.1996.76.6.4152

Tiriac, A., Del Rio-Bermudez, C., & Blumberg, M. S. (2014). Self-Generated Movements with "Unexpected" Sensory Consequences. *Current Biology*, *24*(18), 2136–2141. https://doi.org/10.1016/j.cub.2014.07.053

Tomchek, S. D., & Dunn, W. (2007). Sensory processing in children with and without autism: A comparative study using the short sensory profile. *The American Journal of Occupational Therapy*, *61*(2), 190–200.

Tonacci, A., Billeci, L., Tartarisco, G., Ruta, L., Muratori, F., Pioggia, G., & Gangemi, S. (2017). Olfaction in autism spectrum disorders: A systematic review. *Child Neuropsychology*, *23*(1), 1–25.

Tononi, G., & Cirelli, C. (2006). Sleep function and synaptic homeostasis. *Sleep Medicine Reviews*, *10*(1), 49–62. https://doi.org/10.1016/j.smrv.2005.05.002

Tononi, G., & Cirelli, C. (2014). Sleep and the Price of Plasticity: From Synaptic and Cellular Homeostasis to Memory Consolidation and Integration. *Neuron*, *81*(1), 12–34. https://doi.org/10.1016/j.neuron.2013.12.025

Touchette, E., Dionne, G., Forget-Dubois, N., Petit, D., Pérusse, D., Falissard, B., Tremblay, R. E., Boivin, M., & Montplaisir, J. Y. (2013). Genetic and Environmental Influences on Daytime and Nighttime Sleep Duration in Early Childhood. *Pediatrics*, *131*(6), e1874. https://doi.org/10.1542/peds.2012-2284

Trinder, J., Newman, N. M., Le Grande, M., Whitworth, F., Kay, A., Pirkis, J., & Jordan, K. (1990). Behavioural and EEG responses to auditory stimuli during sleep in newborn infants and in infants aged 3 months. *Biological Psychology*, *31*(3), 213–227. https://doi.org/10.1016/0301-0511(90)90035-U

Tzischinsky, O., Meiri, G., Manelis, L., Bar-Sinai, A., Flusser, H., Michaelovski, A., Zivan, O., Ilan, M., Faroy, M., Menashe, I., & Dinstein, I. (2018a). Sleep disturbances are associated with specific sensory sensitivities in children with autism. *Molecular Autism*, *9*(1), 22. https://doi.org/10.1186/s13229-018-0206-8

Tzischinsky, O., Meiri, G., Manelis, L., Bar-Sinai, A., Flusser, H., Michaelovski, A., Zivan, O., Ilan, M., Faroy, M., Menashe, I., & Dinstein, I. (2018b). Sleep disturbances are associated with specific sensory sensitivities in children with autism. *Molecular Autism*, *9*(1), 22. https://doi.org/10.1186/s13229-018-0206-8

Usami, S., Murayama, K., & Hamaker, E. L. (2019). A unified framework of longitudinal models to examine reciprocal relations. *Psychological Methods*, *24*(5), 637.

Uvnäs-Moberg, K., & Field, T. (2004). *Touch and Massage in Early Child Development*.

Uvnäs-Moberg, K., & Handlin, L. (2015). Self-soothing behaviors with particular reference to oxytocin release induced by non-noxious sensory stimulation. *Frontiers in Psychology*, *5*, 116675.

Vallat, R., & Walker, M. P. (2021). An open-source, high-performance tool for automated sleep staging. *eLife*, *10*, e70092. https://doi.org/10.7554/eLife.70092

Van de Cruys, S., Evers, K., Van der Hallen, R., Van Eylen, L., Boets, B., de-Wit, L., & Wagemans, J. (2014). Precise Minds in Uncertain Worlds: Predictive Coding in Autism. *Psychological Review*, *121*, 649–675. https://doi.org/10.1037/a0037665

Van Etten, H. M., Kaur, M., Srinivasan, S. M., Cohen, S. J., Bhat, A., & Dobkins, K. R. (2017). Increased Prevalence of Unusual Sensory Behaviors in Infants at Risk for, and Teens with, Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*, *47*(11), 3431–3445. https://doi.org/10.1007/s10803-017-3227-9

Van Rossum, G., & Drake, F. L. (2009). *Python 3 Reference Manual*. CreateSpace.

Van Someren, E. J., Cirelli, C., Dijk, D.-J., Van Cauter, E., Schwartz, S., & Chee, M. W. (2015). Disrupted sleep: From molecules to cognition. *Journal of Neuroscience*, *35*(41), 13889–13895.

Vasak, M., Williamson, J., Garden, J., & Zwicker, J. (2015). Sensory Processing and Sleep in Typically Developing Infants and Toddlers. *American Journal of Occupational Therapy*, *69*, 6904220040p1. https://doi.org/10.5014/ajot.2015.015891

Veatch, O. J., Keenan, B. T., Gehrman, P. R., Malow, B. A., & Pack, A. I. (2017). Pleiotropic genetic effects influencing sleep and neurological disorders. *The Lancet Neurology*, *16*(2), 158–170.

Ventura, S., Mathieson, S. R., O'Toole, J. M., Livingstone, V., Ryan, M.-A., & Boylan, G. B. (2022). Electroencephalographic sleep macrostructure and sleep spindles in early infancy. *Sleep*, *45*(1), zsab262. https://doi.org/10.1093/sleep/zsab262

Verhoeff, M. E., Blanken, L. M. E., Kocevska, D., Mileva-Seitz, V. R., Jaddoe, V. W. V., White, T., Verhulst, F., Luijk, M. P. C. M., & Tiemeier, H. (2018). The bidirectional association between sleep problems and autism spectrum disorder: A population-based cohort study. *Molecular Autism*, *9*(1), 8. https://doi.org/10.1186/s13229-018-0194-8

Verma, P., & Baisakhiya, S. (2021). Study of sleep spindle and K-complex characteristics on EEG during sleep in full-term infants from 2 weeks to 12 months of age. *National Journal of Physiology, Pharmacy and Pharmacology*, *11*(11), 1221–1224.

Volgushev, M., Chauvette, S., Mukovski, M., & Timofeev, I. (2006). Precise long-range synchronization of activity and silence in neocortical neurons during slow-wave sleep. *Journal of Neuroscience*, *26*(21), 5665–5672.

von Holst, E., & Mittelstaedt, H. (1950). Das Reafferenzprinzip. *Naturwissenschaften*, *37*(20), 464–476. https://doi.org/10.1007/BF00622503

Vyazovskiy, V. V., Borbely, A., & Tobler, I. (2000). Fast track: Unilateral vibrissae stimulation during waking induces interhemispheric EEG asymmetry during subsequent sleep in the rat. *Journal of Sleep Research*, *9*(4), 367–371.

Vyazovskiy, V. V., & Harris, K. D. (2013). Sleep and the single neuron: The role of global slow oscillations in individual cell rest. *Nature Reviews Neuroscience*, *14*(6), 443–451. https://doi.org/10.1038/nrn3494

Wang, G., Grone, B., Colas, D., Appelbaum, L., & Mourrain, P. (2011). Synaptic plasticity in sleep: Learning, homeostasis and disease. *Trends in Neurosciences*, *34*(9), 452–463. https://doi.org/10.1016/j.tins.2011.07.005

Warby, S. C., Wendt, S. L., Welinder, P., Munk, E. G. S., Carrillo, O., Sorensen, H. B. D., Jennum, P., Peppard, P. E., Perona, P., & Mignot, E. (2014). Sleep-spindle detection: Crowdsourcing and evaluating performance of experts, non-experts and automated methods. *Nature Methods*, *11*(4), 385–392. https://doi.org/10.1038/nmeth.2855

Warren, R. A., & Jones, E. G. (1997). Maturation of neuronal form and function in a mouse thalamo-cortical circuit. *Journal of Neuroscience*, *17*(1), 277–295.

Wei, L., Ventura, S., Mathieson, S., Boylan, G. B., Lowery, M., & Mooney, C. (2022). Spindle-AI: Sleep Spindle Number and Duration Estimation in Infant EEG. *IEEE Transactions on Biomedical Engineering*, *69*(1), 465–474. https://doi.org/10.1109/TBME.2021.3097815

Wei, P.-P., Hunter, S. K., & Ross, R. G. (2017). Sleep Spindles and Auditory Sensory Gating: Two Measures of Cerebral Inhibition in Preschool-Aged Children are Strongly Correlated. *Colorado Journal of Psychiatry & Psychology*, *2*(1), 75.

Weissbluth, M. (1995). Naps in children: 6 months–7 years. *Sleep*, *18*(2), 82–87.

Weitzman, E. D., & Kremen, H. (1965). Auditory evoked responses during different stages of sleep in man. *Electroencephalography and Clinical Neurophysiology*, *18*(1), 65–70.

Wendt, S. L., Welinder, P., Sorensen, H. B. D., Peppard, P. E., Jennum, P., Perona, P., Mignot, E., & Warby, S. C. (2015). Inter-expert and intra-expert reliability in sleep spindle scoring. *Clinical Neurophysiology*, *126*(8), 1548–1556. https://doi.org/10.1016/j.clinph.2014.10.158

Werth, E., Achermann, P., Dijk, D.-J., & Borbély, A. A. (1997). Spindle frequency activity in the sleep EEG: individual differences and topographical distribution. *Electroencephalography and Clinical Neurophysiology*, *103*(5), 535–542.

Whitehead, K., Meek, J., & Fabrizi, L. (2018). Developmental trajectory of movement-related cortical oscillations during active sleep in a cross-sectional cohort of pre-term and full-term human infants. *Scientific Reports*, *8*(1), 17516.

Wigham, S., Rodgers, J., South, M., McConachie, H., & Freeston, M. (2015). The Interplay Between Sensory Processing Abnormalities, Intolerance of Uncertainty, Anxiety and Restricted and Repetitive Behaviours in Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*, *45*(4), 943–952. https://doi.org/10.1007/s10803-014-2248-x

Williams, H. L., Tepas, D. I., & Morlock, H. C. (1962). Evoked Responses to Clicks and Electroencephalographic Stages of Sleep in Man. *Science*, *138*(3541), 685–686. https://doi.org/10.1126/science.138.3541.685

Williams, Z. J., Failla, M. D., Davis, S. L., Heflin, B. H., Okitondo, C. D., Moore, D. J., & Cascio, C. J. (2019). Thermal perceptual thresholds are typical in autism spectrum disorder but strongly related to intra-individual response variability. *Scientific Reports*, *9*(1), 12595.

Wimmer, R. D., Astori, S., Bond, C. T., Rovó, Z., Chatton, J.-Y., Adelman, J. P., Franken, P., & Lüthi, A. (2012). Sustaining Sleep Spindles through Enhanced SK2-Channel Activity Consolidates Sleep and Elevates Arousal Threshold. *The Journal of Neuroscience*, *32*(40), 13917. https://doi.org/10.1523/JNEUROSCI.2313-12.2012

Wintler, T., Schoch, H., Frank, M. G., & Peixoto, L. (2020). Sleep, brain development, and autism spectrum disorders: Insights from animal models. *Journal of Neuroscience Research*, *98*(6), 1137–1149. https://doi.org/10.1002/jnr.24619

Wolff, J. J., Dimian, A. F., Botteron, K. N., Dager, S. R., Elison, J. T., Estes, A. M., Hazlett, H. C., Schultz, R. T., Zwaigenbaum, L., & Piven, J. (2019). A longitudinal study of parent-reported sensory

responsiveness in toddlers at-risk for autism. *Journal of Child Psychology and Psychiatry*, *60*(3), 314–324.

Wood, E. T., Cummings, K. K., Jung, J., Patterson, G., Okada, N., Guo, J., O'Neill, J., Dapretto, M., Bookheimer, S. Y., & Green, S. A. (2021). Sensory over-responsivity is related to GABAergic inhibition in thalamocortical circuits. *Translational Psychiatry*, *11*(1), 39. https://doi.org/10.1038/s41398-020-01154-0

Wu, Z., Huang, S., Zou, J., Wang, Q., Naveed, M., Bao, H., Wang, W., Fukunaga, K., & Han, F. (2020). Autism spectrum disorder (ASD): Disturbance of the melatonin system and its implications. *Biomedicine & Pharmacotherapy*, *130*, 110496. https://doi.org/10.1016/j.biopha.2020.110496

Wulbrand, H., McNamara, F., & Thach, B. T. (1998). Suppression of σ Spindle Electroencephalographic Activity as a Measure of Transient Arousal after Spontaneous and Occlusion-Evoked Sighs and Startles. *Pediatric Research*, *44*(5), 767–773. https://doi.org/10.1203/00006450-199811000-00021

Yeung, L. H. J., & Thomacos, N. (2020). Assessments of sensory processing in infants and children with autism spectrum disorder between 0–12 years old: A scoping review. *Research in Autism Spectrum Disorders*, *72*, 101517. https://doi.org/10.1016/j.rasd.2020.101517

Yüzgeç, Ö., Prsa, M., Zimmermann, R., & Huber, D. (2018). Pupil size coupling to cortical states protects the stability of deep sleep via parasympathetic modulation. *Current Biology*, *28*(3), 392–400.

Zadorozhny, B. S., Petrides, K. V., Jongerling, J., Cuppello, S., & van der Linden, D. (2024). Assessing the temporal stability of a measure of trait emotional intelligence: Systematic review and empirical analysis. *Personality and Individual Differences*, *217*, 112467. https://doi.org/10.1016/j.paid.2023.112467

Zhang, L., Huang, Y., Zhang, Y., Xin, W., Shao, Y., & Yang, Y. (2019). Enhanced high-frequency precuneus-cortical effective connectivity is associated with decreased sensory gating following total sleep deprivation. *NeuroImage*, *197*, 255–263. https://doi.org/10.1016/j.neuroimage.2019.04.057

Zyphur, M. J., Allison, P. D., Tay, L., Voelkle, M. C., Preacher, K. J., Zhang, Z., Hamaker, E. L., Shamsollahi, A., Pierides, D. C., Koval, P., & Diener, E. (2020). From Data to Causes I: Building A General Cross-Lagged Panel Model (GCLM). *Organizational Research Methods*, *23*(4), 651–687. https://doi.org/10.1177/1094428119847278

Appendix A. Descriptive statistics by autism likelihood and diagnostic status

Table A. 1 Autism Diagnostic Observation Schedule calibrated severity scores; EL: Elevated likelihood; ELC: Early learning component; SOL: Sleep onset latency; TL: Typical likelihood; TSI: Tactile suppression index;

	Autism likelihood status		**EL group autism diagnosis**	
	TL	**EL**	**EL-ASD-**	**EL-ASD+**
5-month visit				
n	25	66	48	10
Age in Days	178.42 (13.29)	176.08 (19.61)	175.26 (19.99)	174.50 (18.47)
Sex (M:F)	18:7	35:31	24:24	6:4
ADOS CSS	1.55 (0.69)	3.10 (2.25)	2.83 (1.92)	3.89 (2.80)
Mullen ELC	85.08 (9.704)	83.55 (10.943)	84.72 (11.78)	82.60 (15.01)
Number of awakenings	2.44 (1.47)	2.00 (1.48)	1.89 (1.46)	2.30 (1.95)
SOL	11.15 (10.10)	12.42 (10.35)	10.88 (8.98)	15.62 (13.43)
10-month visit				
n	22	82	62	10
Age in Days	318.77 (15.76)	318.04 (14.16)	319.57 (15.05)	319.40 (9.24)
Sex (M:F)	15:7	46:36	34:28	6:4
ADOS CSS	1.53 (0.61)	2.97 (2.20)	2.73 (1.83)	3.89 (3.14)
Mullen ELC	90.09 (11.05)	87.56 (14.66)	87.61 (14.76)	87.80 (12.53)
Number of awakenings	1.27 (1.08)	1.95 (1.37)	1.95 (1.40)	2.00 (1.76)
SOL	7.92 (6.19)	11.45 (7.51)	10.08 (6.42)	16.25 (10.33)
TSI	0.1412 (0.1407)	-0.0088 (0.2120)	-0.0098 (0.2246)	-0.0320 (0.1486)
14-month visit				
n	19	84	65	11
Age in Days	448.16 (17.62)	449.56 (18.90)	451.56 (19.38)	443.82 (15.68)
Sex (M:F)	12:7	45:39	34:31	7:4
ADOS CSS	1.59 (0.71)	2.96 (2.16)	2.69 (1.79)	4.00 (2.98)
Mullen ELC	80.26 (10.84)	76.29 (12.69)	77.06 (13.81)	69.27 (7.28)
Number of awakenings	1.00 (1.45)	1.87 (1.46)	1.72 (1.33)	2.73 (1.74)
SOL	6.46 (7.25)	13.18 (11.40)	12.59 (12.25)	17.29 (10.15)

Appendix B. Low Threshold Questions

All questions included for the calculation of the variable Low Threshold are listed here. In Chapter 2 and 3, the first version of the Infant/Toddler Sensory profile (ITSP) was used. At the 5 month timepoint caregivers completed the 0-7 month version (Table A.2). At the 10- and 14-month timepoint caregivers completed the 7-36 month version (Table A.3). In Chapter 5, the second version of the same questionnaire was used: the Sensory Profile-2 (SP-2). Caregivers completed the 7-36-month version of the SP-2 (Table A.4).

Table A.2 Questions from the Infant/Toddler Sensory Profile of the sensory sensitivity and avoidance quadrants 0-7 months. Question 5 (in red) was removed for the analysis

Quadrant	Item number	Question	Modality
Sensory sensitivity	4.	My child's behaviour deteriorates when the schedule changes	General
	5.	My child has difficulty getting to sleep and is easily awakened	General
	6.	My child is irritable when compared to same age children	General
	13.	My child startles easily at sound compared to other children the same age	Auditory
	14.	My child is distracted and/or has difficulty eating in noisy environments	Auditory
	19.	My child gets fussy when exposed to bright lights	Visual
	21.	My child startles at own reflection in the mirror	Visual
	25.	My child becomes agitated when having hair washed	Tactile
	27.	My child is distressed when having nails trimmed	Tactile
	33.	My child becomes upset when placed on their back to change diapers	Vestibular
	34.	Riding in the car upsets my child	Vestibular
	36.	My child cries or fusses whenever I try to move him/her	Vestibular
Avoidance	22.	My child avoids looking at toys	Visual
	24.	My child resists being held	Tactile
	26.	My child avoids getting face/nose wiped	Tactile
	28.	My child resists being held	Tactile
	35.	My child resists having head tipped back during bathing	Vestibular

Table A.3 Questions from the Infant/Toddler Sensory Profile of the sensory sensitivity and avoidance quadrants 7 – 36 months.

Quadrant	Item number	Question	Modality
Sensory sensitivity	1.	My child's behaviour deteriorates when the schedule changes	General
	8.	My child startles easily at sound compared to other children the same age	Auditory
	9.	My child is distracted and/or has difficulty eating in noisy environments	Auditory
	22.	My child becomes agitated when having hair washed	Tactile
	24.	My child is distressed when having nails trimmed	Tactile
	26.	My child is upset by changes in the bath water temperature, from one bath to the next.	Tactile
	28.	My child becomes upset if own clothing, hands, and/or face are messy	Tactile
	29.	My child gets upset with extreme differences in room temperature (for example, hotter, colder)	Tactile
	30.	My child becomes anxious when walking or crawling on certain surfaces (for example, grass, sand, carpet, tile)	Tactile
	39.	My child becomes upset when placed on back to change diapers	Vestibular
	41.	My child cries or fusses whenever I try to move him/her	Vestibular
Avoidance	2.	My child avoids playing with others.	General
	3.	My child withdraws from situations	General
	11.	My child tries to escape from noisy environments	Auditory
	17.	My child refuses to look at books with me	Visual
	21.	My child resists being held	Tactile
	23.	My child avoids getting face/nose wiped	Tactile
	25.	My child resists being cuddled	Tactile
	27.	My child avoids contact with rough or cold surfaces (for example, squirms, arches, cries.)	Tactile
	40.	My child resists having head tipped back during bathing	Vestibular
	45.	My child refuses all but a few food choices.	Oral
	46.	My child resists having teeth brushed.	Oral
	48.	My child refuses to try new foods	Oral

Table A.4 Questions from the Sensory Profile 2 (7-36 months version) of the sensory sensitivity and avoidance quadrant .

Quadrant	Item number	Question	Modality
Sensory sensitivity	1.	Needs a routine to stay content or calm	General
	2.	Acts in a way that interferes with family schedules	General
	13.	Startles easily at sound compared to same-age children (for example, dog barking, children shouting)	Auditory
	16.	Becomes upset or tries to escape from noisy settings	Auditory
	26.	Becomes upset when having nails trimmed.	Touch
	31.	Pulls all clothing or resists getting clothing on	Touch
	34.	Becomes anxious when walking or crawling on certain surfaces (for example, grass, sand, carpet, tile)	Touch
	39.	Becomes upset when placed on the back (for example, at changing times)	Movement
	41.	Fusses when moved around (for example, at changing times)	
	44.	Prefers one texture of food (for example, smooth, crunchy)	Oral
	48.	Has difficulty weaning to chunky foods	Oral
	52.	Is fussy or irritable	Behavioural
Avoidance	3.	Resists playing among other children	General
	10.	Gets anxious in new situations	General
	27.	Resists being cuddled	Touch
	28.	Is upset when moving among spaces with very different temperatures (for example, colder, warmer)	Touch
	29.	Withdraws from contact with rough, cold, or sticky surfaces (for example, carpet, countertops)	Touch
	33.	Becomes upset if own clothing, hands, or face are messy	Touch
	35.	Withdraws from unexpected touch	Touch
	42.	Shows a clear dislike for all but a few food choices	Oral
	49.	Has temper tantrums	Behavioural
	53.	Is bothered by new settings	Behavioural
	54.	Becomes so upset in new settings that it's hard to calm down	Behavioural

Appendix C. Chapter 3: variable distributions and outliers

Table A.5 Datapoints with a z-score above 3. Values in red were Winsorized. Awa: Night awakenings; SOL: Sleep Onset Latency; LT: Low Threshold

	z-score	Original value	Winsorized value
Awa 5 months	/		
Awa 10 months	5.404	10	7
Awa 14 months	3.429	7	/
SOL 5 months	5.896 3.861	90 63.33	48.67 47.67
SOL 10 months	3.202	34.17	/
SOL 14 months	5.849 3.221	85.33 52.5	53.5
LT 5 months	3.684	3.625	/
LT 10 months	3.510 3.073	4 3.739	/
LT 14 months	3.39955	4	/

Table A.6 Normality, skewness and kurtosis of all continuous variables included in the models. Outliers have been Winsorized

	Mean	**Variance**	**Skewness**	**Kurtosis**	**Normalilty test**	
					W	**p-value**
Awa_5	2.19	2.10	0.40	-0.47	0.95	0.001
Awa_10	1.91	1.84	0.88	1.41	0.92	<0.001
Awa_14	1.80	2.30	1.15	1.35	0.89	<0.001
SOL_5	12.08	103.77	1.70	3.70	0.83	<0.001
SOL_10	10.70	53.71	0.80	0.29	0.95	<0.001
SOL_14	11.94	120.71	1.57	2.57	0.84	<0.001
LT_5	1.84	0.24	0.90	1.26	0.95	0.001
LT_10	1.90	0.36	1.28	1.63	0.90	<0.001
LT_14	1.99	0.35	1.16	0.88	0.90	<0.001

Appendix D. Topography of sigma and delta power in the pilot sample

Topography of sigma and delta in the first 14 recordings, used to justify regions of interest in the pre-registration.

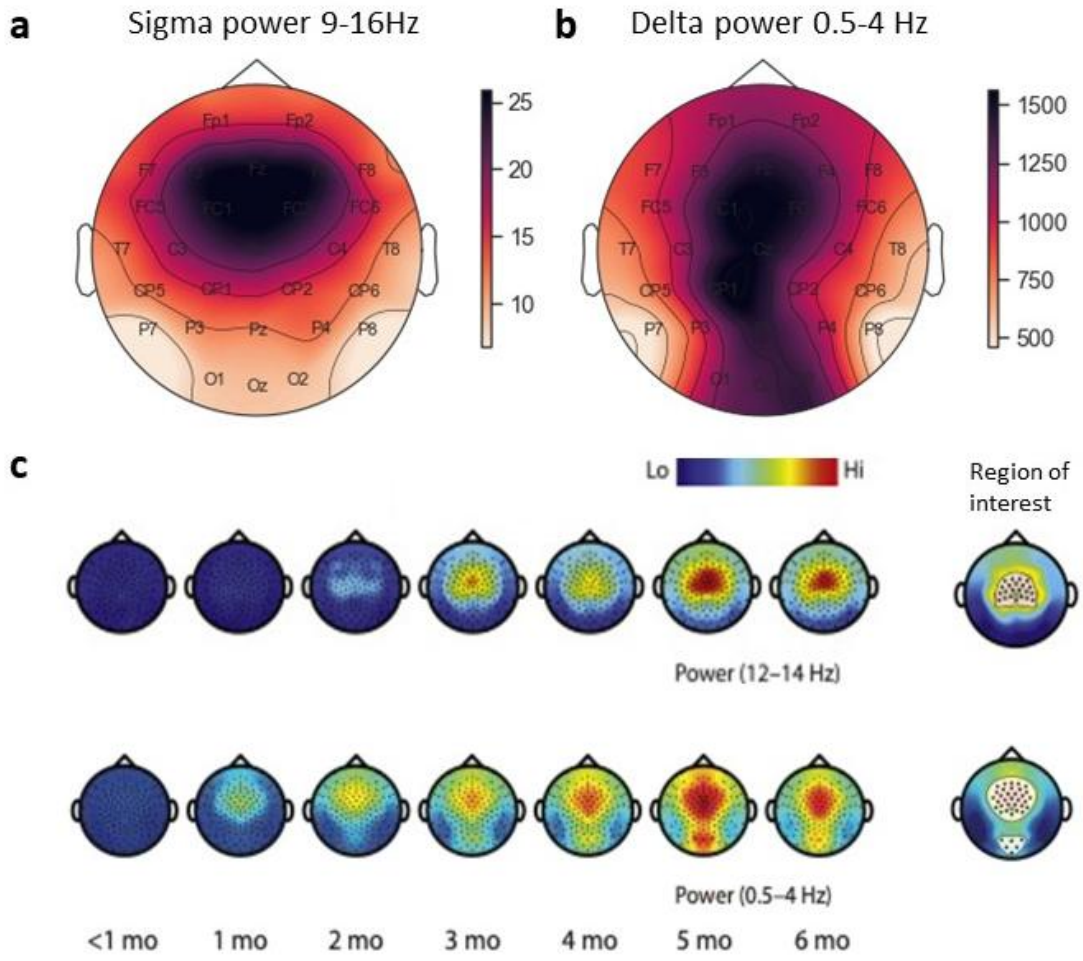

Figure A.1 Comparison of topography for sigma and delta power topography in the pilot sample of this study and infants 0-6 months old. A) Sigma power (9-16 Hz) in N2 and N3 in the pilot sample (n = 14). B) Delta power (0.5-4 Hz) in N2 and N3 in the pilot sample. C) Figure adapted from Sokoloff et al. (2021) showing the sigma and delta power changes from 0-6 months of age.

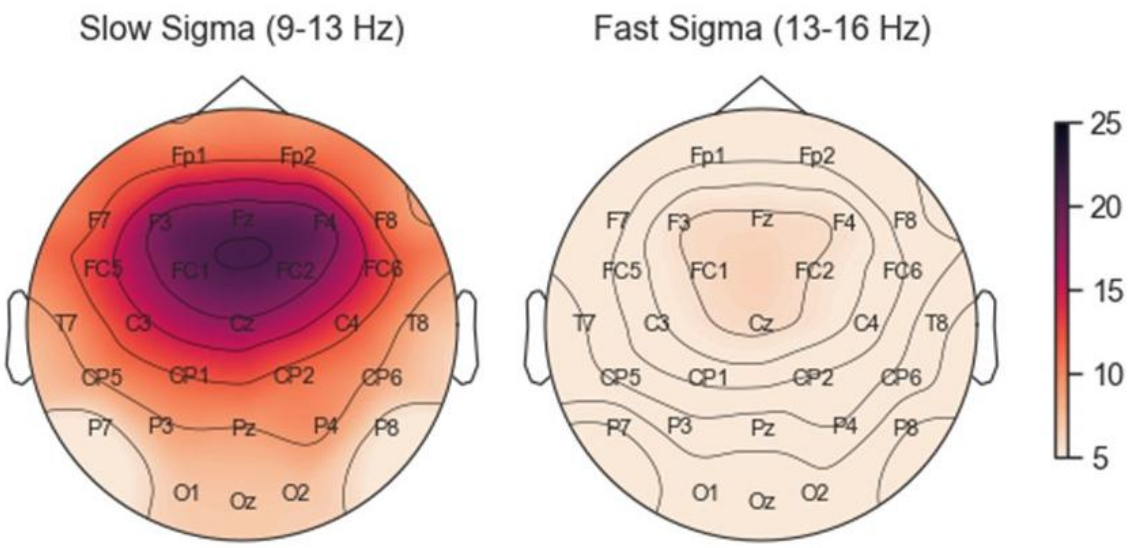

Figure A.2 Comparison of the topography of slow and fast sleep spindle activity (9-13 Hz and 13-16 Hz respectively). Average of the pilot sample (n=14).

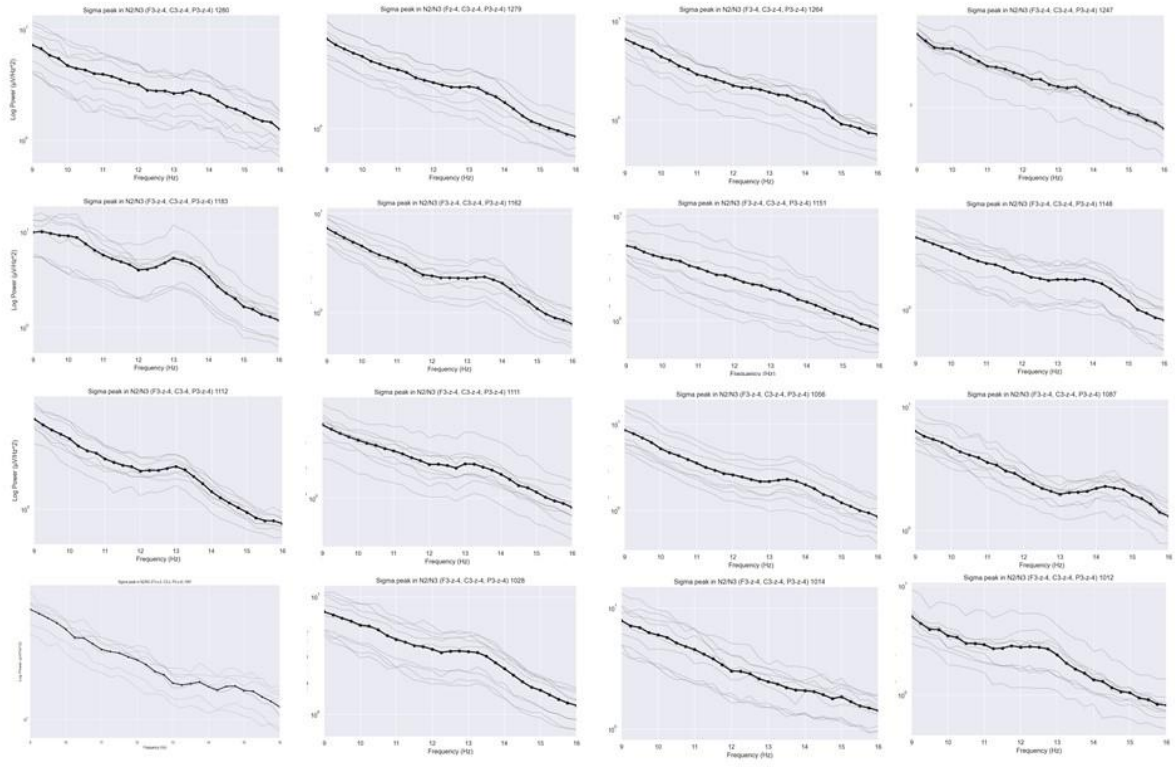

Figure A.3 Individual sigma peaks plotted from 9-16 Hz. Grey lines are individual channels (F3, F4, C3, C4, P3, P4), black line in the average of those channels.

Appendix E. K-complex likelihood S1 and S2

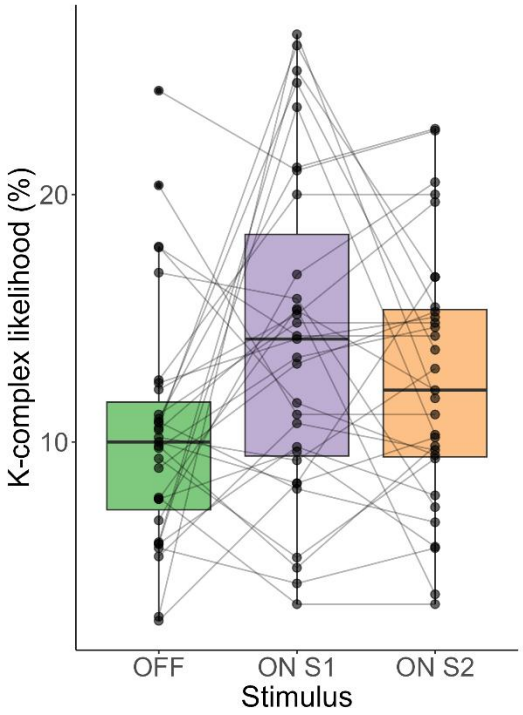

Figure A. 4 K-complex likelihood in the absence of stimulation (OFF), after S1 (ON S1) and S2 (ON S2).

Appendix F. AI, SWA and Sigma across sleep stages

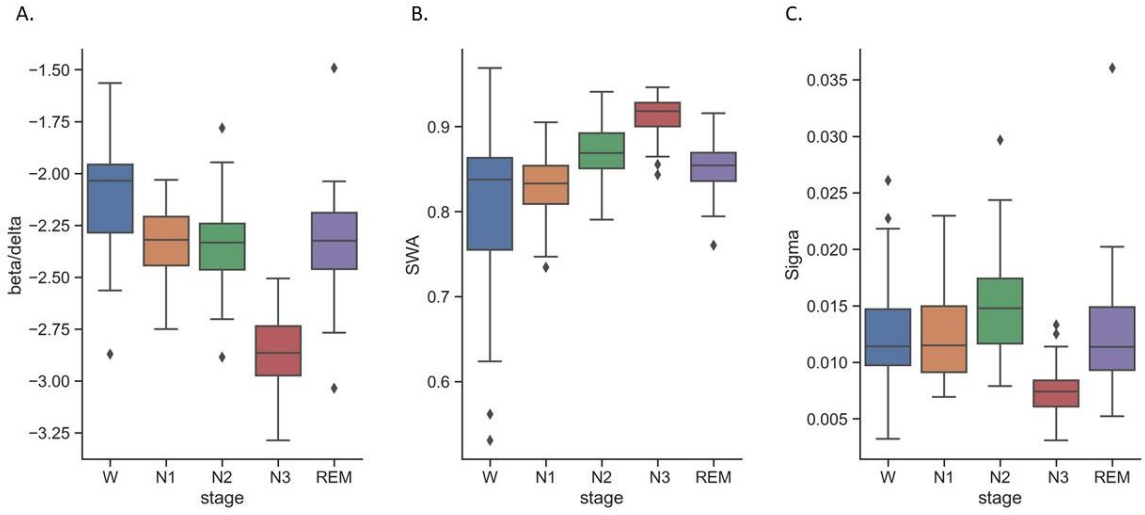

Figure A.5 ***A.*** *Activation index (beta/delta),* ***B****. Slow wave activity (SWA) and* ***C****. sigma power across sleep stages.*

Appendix G. Chapter 5: Outliers

Table A.7 Outliers and Winsorized values (in red) of Chapter 5.

	z-score	Original value	Winsorized value
Sleep duration SPT	3.310	127	/
Arousal density	4.36	0.422	0.261
Spindle density N2	3.614 3.416	4.723 4.538	3.599 3.499
Median spindle frequency N2	-3.834	9.819	11.184
Median SWA N3	3.227 3.592	4062.31 4309.04	/ /
Median Sigma N2	3.141	42.427	/