Characterisation of online, remote neuropsychological test performance in people with and without subjective cognitive decline

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Thesis portfolio abstract

Subjective cognitive decline (SCD) may represent a preclinical stage of dementia for a subsample of people. Detection of the very earliest cognitive changes in preclinical dementia may identify those at risk of further decline. The development of online, remote neuropsychological assessment paradigms may provide a cost-effective method of assessing and monitoring SCD. However, their psychometric properties must be established. This thesis aimed to evaluate the utility of online, remote neuropsychological testing for assessing and monitoring SCD. A meta-analysis was conducted to synthesise the research into episodic memory performance by people with SCD, to begin to characterise a "cognitive profile" of SCD which may be detected using neuropsychological assessment. An empirical study was then conducted to (i) assess the test-retest reliability of a novel, online neuropsychological test battery (NeurOn), completed remotely by participants with and without SCD (Non-SCD), and (ii) investigate group differences in performance. The results of the present research indicate that SCD is associated with significant episodic memory impairment compared to Non-SCD. The empirical study found evidence for moderate reliability of online and remote assessment using specific NeurOn tests (Sustained Attention to Response Test, Picture Recognition, and Trail-Making Test A) in both groups. However, no group differences in neuropsychological test performance were identified. Limitations of the present research are discussed along with recommended future directions. Overall, the findings suggest that SCD is associated with subtle cognitive impairment, and online, remote neuropsychological assessment offers a reliable method for assessing and monitoring SCD.

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Dedication and acknowledgements

This thesis is dedicated to the memory of my mother, Jennifer Watt (12th January 1963 – 12th November 2021), who passed away two months after I started the Doctorate of Clinical Psychology. Her unwavering belief in my ability to achieve whatever I set out to do was instilled in me and is the reason I am where I am today.

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Finally, I would like to thank everyone who participated in this research.

Declaration

Material from the ClinPsyD Thesis Proposal assignment has been adapted and used throughout this thesis.

CHAPTER ONE: Introduction to the thesis portfolio

General introduction

Neuropsychological tests are used to measure how well the brain is functioning. They play a key part in the assessment and monitoring of neurological conditions such as stroke, brain injury, and dementia; and in informing evidence-based treatments of increasingly larger groups of people and mental health conditions across the lifespan (Sperling et al., 2023). While neuropsychological testing has traditionally been conducted in-person in a clinic environment, there is increased interest in evaluating the utility of remote neuropsychological assessment paradigms. Online, remote neuropsychological testing offers potential benefits to in-person assessment, for example, by reducing the cost and time required for assessments (Davis et al., 2014), and improving access for people living in remote or under-served areas, or those unable to attend in-person assessments due to health conditions (Adjorlolo, 2015; Barton et al., 2011; Brearly et al., 2017; Wadsworth et al., 2018). Further, online neuropsychological testing has the potential to enable the recruitment of significantly larger and more representative cohorts of people within clinical research (Castanho et al., 2014; Feenstra et al., 2017; Miller & Barr, 2017; Tailby et al., 2020).

Online, remote neuropsychological assessment (teleneuropsychology) could be particularly valuable for the assessment and monitoring of people in the general adult population who experience subjective cognitive decline (SCD). Subjective cognitive decline has been defined for research purposes as "self-experienced persistent decline in cognitive capacity in comparison with a previously normal status and unrelated to an acute event" in the context of "normal age-, gender-, and education-adjusted performance on standardised cognitive tests, which are used to classify mild cognitive impairment (MCI) or prodromal Alzheimer's disease" (Jessen et al., 2014). Since the concept of SCD was first suggested an emerging literature has developed to understand this better. Research suggests the prevalence

of SCD may be as high as 56% in adults over the age of 65 (Garcia-Ptacek et al., 2016; Jonker et al., 1999) and people are increasingly seeking medical advice for SCD (Jessen et al., 2020). Although most people who experience SCD do not progress to MCI or dementia, they may be at double the risk of doing so compared to people without SCD (Mitchell et al., 2014); thus suggesting that, for a small cohort of people, SCD may indicate prodromal dementia. Evidence suggests that approximately 6.6% of people with SCD will progress to MCI and 2.3% to dementia, per year (Mitchell et al., 2014). Given the large numbers involved, significant testing resources would be required to assess and monitor everyone with SCD. However, online, remote neuropsychological assessment could offer a lower cost alternative for monitoring this group of people and a reduced burden on healthcare resources.

This thesis examines the utility of online, remote neuropsychological assessment for assessing and monitoring cognitive ability in people with SCD. The thesis contains the following two studies which seek to explore this question:

- a systematic review and meta-analysis of episodic memory test performance in people with SCD to investigate whether there is a subtle "cognitive profile" of SCD which may be detected using detailed neuropsychological assessment, and
- an empirical study to investigate the reliability of online, remote neuropsychological assessment for monitoring SCD. This study also explores whether there are group differences in performance on online neuropsychological tests between people with and without SCD.

Chapter One provides an introduction to teleneuropsychology including its potential benefits and challenges, an overview of research into the validity and reliability of online neuropsychological test batteries, and a discussion on the relevance of teleneuropsychology to SCD. Chapter One concludes with a summary of the thesis aims.

Teleneuropsychology

Teleneuropsychology refers to the remote provision of neuropsychological assessment and intervention services through the use of telecommunication technologies (Van Den Broek et al., 2022). Although interest in teleneuropsychology preceded the COVID-19 pandemic, the pandemic greatly increased the need to consider alternative methods for undertaking clinical neuropsychology work. In April 2020, the British Psychological Society Division of Neuropsychology (BPS DON) released guidelines on the use of remote neuropsychology during the pandemic (BPS DON, 2020). In their guidance, the BPS DON provided support for the use of remote technologies for neuropsychological services while highlighting the need to develop the evidence base around comparability of remote and in-person assessments.

The types of technologies which have been employed for teleneuropsychology services largely involve telephone-based assessments and videoconferencing (Sperling et al., 2023). However, there is emerging research into the feasibility of remote, web-based neuropsychological assessment, which ranges from the use of structured computerised tests without supervision to brief cognitive assessments using smartphones (Van Patten, 2021). Initial studies investigating the feasibility of unsupervised (i.e. where the patient/participant is unsupervised by a researcher/clinician during test completion), online neuropsychological test paradigms have reported good reliability and validity of tests (Chaytor et al., 2021; Feenstra et al., 2018; Singh et al., 2021). However, more research is required to develop the evidence base before it can be adopted into clinical practice (Sperling et al., 2023; Van Patten, 2021). The potential benefits and challenges associated with teleneuropsychology, including remote, online neuropsychological assessment, are outlined below.

Potential benefits of remote, online neuropsychology

The need to rapidly adopt teleneuropsychology during the COVID-19 pandemic has fuelled the development and evaluation of remote neuropsychological assessment paradigms. Initial evidence from the introduction of teleneuropsychology during the pandemic showed that telephone-based neuropsychology use led to a reduction in appointment no-shows and cancellations within a United States-based neuropsychology service (Caze et al., 2020). This suggested increased accessibility of services and reduced costs associated with missed appointments. The use of telephone- and videoconferencing-based neuropsychological assessment in a National Health Service (NHS) neuropsychology department during the pandemic similarly led to a reduction in did-not-attend discharges; and clinicians, service users, and referrers reported high acceptability of the process (Sumpter et al., 2023). Such alternatives to in-person assessment may help to reduce health inequalities for people from underserved backgrounds who face barriers to accessing healthcare (Adjorlolo, 2015; NHS, 2020a, 2022; Sperling et al., 2023; Teager et al., 2023; Wadsworth et al., 2018). The COVID-19 pandemic exacerbated existing health inequalities (NHS, 2020b), making improved and equitable access to healthcare key priorities for the NHS (NHS, 2020a).

The integration of fully remote and unsupervised online neuropsychological assessment paradigms within clinical practice and research may offer further potential advantages which have been summarised elsewhere (Feenstra et al., 2017; Sperling et al., 2023; Van Patten, 2021). For example, they would allow for the recruitment of significantly larger and more diverse cohorts of people for research studies on cognitive functioning (Caze et al., 2020; Messler et al., 2023); and the use of computerised testing offers greater accuracy and objectivity of scoring, standardisation of stimulus presentation, and automation of comparison of scores to normative data (Feenstra et al., 2017; Van Patten, 2021). Computerised assessment also has the potential to capture richer data than is possible using

pen-and-paper tests, providing more nuanced information than just an ‘overall score’. These have important clinical benefits. The combination of larger samples for research with increased automative capabilities has the potential to provide greater evidence which, in turn, enhances safety and effectiveness of clinical practice.

Remote, unsupervised online assessment may additionally increase accessibility by removing time constraints for participants who would be unable to complete assessments during typical working hours (Feenstra et al., 2017). Clinically, integrating unsupervised neuropsychological assessment reduces costs associated with clinician time, training, and travel, therefore reducing the burden on healthcare services (Feenstra et al., 2017), and may reduce waiting times for patients to be able to access assessments (Pritchard et al., 2020; Sperling et al., 2023).

Improving accessibility of neuropsychological assessment services may help to address the documented underdiagnosis rates of conditions including dementia, mild cognitive impairment (MCI), and attention deficit hyperactivity disorder (Lin et al., 2021; Sperling et al., 2023; Young et al., 2021), for which there are numerous potential benefits associated with timely diagnosis (Dubois et al., 2016; Young et al., 2021). Indeed, access to timely diagnosis is a priority of the NHS (National, 2018; NHS, 2019). Data from NHS England suggests that the current rate of dementia diagnosis for people aged 65+ is 63.1% (NHS Digital, 2023) and the average waiting time between referral and diagnosis increased in the wake of the pandemic by 36% to 17.7 weeks (Royal College of Psychiatrists, 2022). The Chief Medical Officer’s 2023 report, ‘Health in an Ageing Society‘, highlights that the proportion of older adults is disproportionately higher in rural areas of England and the disparity is projected to increase in the coming decades (Whitty, 2021). Therefore, it is imperative that healthcare services plan how to effectively meet the needs of this population going forward. Online, remote neuropsychological assessment could help to meet the

increasing need for access to neuropsychological assessment services for older adults living in rural locations who may be affected by reduced mobility as well as poorer transport links (Barton et al., 2011; Sumpter et al., 2023; Whitty, 2021).

Potential challenges for integrating online, remote neuropsychology

Despite the potential advantages of online, remote neuropsychological assessment, it is important to also consider challenges to incorporating it into practice. Both clinicians and service users may have understandable concerns which will reduce the likelihood of teleneuropsychology being adopted. There may be technical obstacles either for the clinician/researcher or the patient, for example, outdated software, poor internet quality, or misunderstandings of instructions (Schmand, 2019). Van Patten (2021) outlines potential concerns around security and validity, but points out that advances in technology can be harnessed to counter these, for example, using biometrics to verify user identities and incorporating simple, user-friendly designs to minimise the need for computer familiarity on the part of patients. Performance and willingness to complete tests remotely may be associated with computer literacy (Boucher et al., 2023; Van Patten, 2021), therefore, research into the feasibility of remote, online neuropsychological assessment should consider the impact of computer literacy. Additionally, some cognitive tasks may not be easily adapted to a computerised format, such as those assessing higher-order executive functioning.

Researchers have highlighted how disparities in access to technology may mean some people are further excluded from neuropsychology services if they require technology access (Fox-Fuller et al., 2022; Sperling et al., 2023). Other concerns include a lack of control over the testing environment and access to help/additional instruction from a clinician (Feenstra et al., 2017; Marra et al., 2020), and sensory difficulties impacting the ability to complete computerised tests (Feenstra et al., 2017; Sumpter et al., 2023). Further, while surveys have

shown good levels of acceptability of teleneuropsychology by patients (Appleman et al., 2021; Lacritz et al., 2020; Royal College of Psychiatrists, 2022; Sumpter et al., 2023) some people prefer in-person appointments (Lacritz et al., 2020; Stelmokas et al., 2023; Sumpter et al., 2023). Therefore, it will be important to consider patient choice when adopting teleneuropsychology services clinically.

An important concern for clinicians about the adoption of teleneuropsychology is a lack of evidence for the reliability and validity of computerised tests and comparability with their pen-and-paper equivalents (Schmand, 2019; Van Patten, 2021). Therefore, it is vital that more research is conducted into the psychometric properties of remote neuropsychological assessment paradigms (Sperling et al., 2023; Van Patten, 2021).

The solution to the above concerns may be to adopt an integrated model of neuropsychology which includes teleneuropsychology as an option for service users rather than it fully replacing traditional models, whilst simultaneously developing the evidence base around the reliability and feasibility of online, remote assessment (Sperling et al., 2023; Van Patten, 2021).

Reliability and feasibility of online neuropsychological test batteries

A systematic review of digital (including remote, in-person, supervised and unsupervised) cognitive assessment tools for preclinical Alzheimer's disease found that research so far suggests promising validity against traditional assessment tools (Öhman et al., 2021). However, the authors identified a need for more data on the validity of remote assessment paradigms.

A recent study using an online computerised cognitive test battery (via the Cognitron platform) in a traumatic brain injury (TBI) population, which included an unsupervised condition, showed good feasibility and comparability to standard neuropsychological

assessments (Del Giovane et al., 2023). The assessment battery was sensitive to cognitive impairment due to TBI in both the supervised and unsupervised testing conditions. The authors concluded that the use of online cognitive assessment can support longitudinal cognitive assessment of people with TBI to best identify those in need of further assessment and intervention.

Various tools have been developed or adapted for online, remote, unsupervised neuropsychological assessment and their psychometric properties assessed. Table 1.1 provides a summary of these. The psychometric properties have been assessed in a variety of clinical and non-clinical populations, and age ranges. Concurrent and convergent validity of specific tests range from low to high. Given the heterogeneity between studies in terms of study populations, tests used, and study designs (e.g. completely unsupervised, home based test completion vs in-clinic with minimal supervision; analysis methods), more data is needed to establish psychometric properties of test batteries with different populations and in different settings, particularly for tests designed to be completed remotely and without supervision (Feenstra et al., 2017; Sperling et al., 2023).

Table 1.1 Psychometric properties of online, remote, unsupervised neuropsychological assessment batteries

Battery	**Citation**	**Cognitive domains assessed**	**Participant sample**	**Results**
TestMyBrain	(Chaytor et al., 2021)	Working memory/attention, processing speed, perceptual reasoning, vocabulary.	People with diabetes aged 18+.	Convergent validity: 0.49 – 0.66 ($p < 0.05$).
The Amsterdam Cognition Scan	(Feenstra et al., 2018)	Attention, processing speed, working memory, verbal learning and memory, visuospatial memory, executive functioning, psychomotor speed.	Cancer patients aged between 18-76 years.	Intraclass correlations: 0.29 – 0.76 ($p < 0.01$). Concurrent validity: 0.36 - 0.70 ($p < 0.001$).
Memoro	(Hansen et al., 2015)	Verbal memory, spatial memory, working memory, processing speed.	Adults aged 50+ without current or previous neurological disease.	Concurrent validity: 0.49 – 0.63 ($p < 0.01$).
CogState	(Maruff et al., 2009)	Processing speed, attention, working memory, learning.	Healthy adults aged between 35-50.	Construct validity: $r = 0.49$ – 0.83.
NeurOn	(Morrissey et al., 2023)	Processing speed, executive functioning, spatial working memory, episodic memory, attentional control, visuospatial ability and spatial orientation.	Healthy adults aged 65+.	Intraclass correlations: 0.51 – 0.75. Concurrent validity: $r = 0.24$ – 0.62.

WebNeuro	(Silverstein et al., 2007)	Sensorimotor, memory, executive functioning, attention, social cognition.	Healthy adults aged between 18-55.	Convergent validity (with a non-web-based computerised test battery): $r = 0.43 – 0.87$.
The TestMyBrain Digital Neuropsychology Toolkit	(Singh et al., 2021)	Working memory/attention, processing speed, memory, executive functioning, perceptual reasoning.	Unknown (anonymised data).	Split-half reliability: 0.68 – 0.99.
Cognitive Function Test	(Trustram Eve & De Jager, 2014)	Episodic memory, processing speed, executive functioning.	Adults aged between 50-65 without dementia or significant memory complaints.	Concurrent validity (total pen and paper x Cognitive Function Test correlations): ($r = 0.75$, $p < 0.0001$).

Relevance to subjective cognitive decline

Subjective cognitive decline (SCD) is the self-experienced perception of a decline in cognitive function in the absence of objective impairment on standardised tests used to detect mild cognitive impairment (MCI) or dementia (Jessen et al., 2014). Evidence suggests that, for a small proportion of people, SCD can indicate an early stage of dementia (Jessen et al., 2014; Mitchell et al., 2014; Pike et al., 2022).

Dementia is the progressive impairment of cognitive function across multiple domains caused by neurodegeneration, which negatively impacts social or occupational function (Arvanitakis et al., 2019). Globally, around 55 million people are living with dementia, and this is projected to rise to 139 million by 2050 (Information obtained from Alzheimer's

Society: https://www.alzheimers.org.uk/about-us/news-and-media/facts-media). Alzheimer's disease is the most common cause of dementia, however there are many types of dementia and it is commonly associated with multiple comorbid neuropathologies (Arvanitakis et al., 2019). The clinical manifestation depends on the type of neuropathology and location of affected brain regions (Matej et al., 2019). Alzheimer's disease usually causes episodic memory impairment due to degeneration of the hippocampus, a brain region involved in learning and memory (Rao et al., 2022).

A major focus of dementia research is the identification of the earliest markers of neurodegenerative disease when interventions (e.g. lifestyle interventions or disease-modifying drug treatments) may be most effective (Azevedo et al., 2023). Alzheimer's disease has a slow and progressive course which begins years before symptoms become apparent (Aisen et al., 2013; Jessen et al., 2014). Clinical trials of drug treatments targeting Alzheimer's disease neuropathology have shown minimal clinical benefit during the symptomatic stages indicating that this stage is too late to halt cognitive decline (Elmaleh et al., 2019). As a result, there is greater emphasis on the detection of earlier markers of prodromal, or "preprodomal" (Jessen et al., 2014) stages of neurodegeneration.

There is evidence that the preclinical stage of Alzheimer's disease is associated with a subjective experience of cognitive decline (Jessen et al., 2014). Therefore, SCD may be an early indicator of risk of later dementia. Further, this group may show subtle cognitive deficits using detailed neuropsychological assessment (Jessen et al., 2014; Wolfsgruber et al., 2020).

More research is needed to understand the neuropsychology of SCD. Since SCD is common among the older adult population, harnessing technology to increase the availability and frequency of detailed neuropsychological assessment through online and remote testing may provide greater understanding of SCD. For example, it will be important to identify

whether there is a “cognitive profile” which suggests increased risk of dementia in people with SCD (Pike et al., 2022). Clinically, for those with additional risk factors of dementia, online, remote neuropsychological assessment could offer a low-cost alternative to in-person assessment and monitoring of SCD. It is, therefore, vital for research to establish the feasibility and reliability of online, remote neuropsychological assessment in people with SCD (Atkins et al., 2022).

Aims of the thesis

This thesis aims to evaluate the utility of online, remote neuropsychological testing for the assessment and monitoring of SCD. The thesis begins by synthesising research into SCD following its operational definition in 2014 to investigate whether there is significant episodic memory impairment, on average, in people with SCD compared to people without SCD (Chapter Two). Many of the studies reporting subtle cognitive deficits in SCD recruited participants via memory clinics (Koppara et al., 2015; Lazarou et al., 2021; Macoir et al., 2019; Wolfsgruber et al., 2020). It is unclear whether presentation at a memory clinic (i.e. implying worry about SCD) is associated with increased risk for subtle cognitive impairment in SCD. Therefore, Chapter Two explores whether recruitment source (medical setting versus community) moderates a potential group difference in memory performance between people with and without SCD. The results of this study will inform hypotheses about whether SCD will show cognitive impairment using detailed neuropsychological assessment.

Chapter Three is an empirical project which assesses the test-retest reliability of a fully remote, online neuropsychological test battery in people with and without SCD. It is unclear whether online, remote neuropsychological assessment shows comparable reliability to ‘gold-standard’ in-person, pen and paper tests (Morrissey et al., 2023). Performance during online testing can be affected by additional factors which may impact reliability of results,

such as computer skills and familiarity, technical issues, cognitive and physical abilities affecting computer use, and lack of supervision and additional instruction (Feenstra et al., 2017). Given the potential wide-ranging benefits to incorporating remote neuropsychological assessment, it is of primary importance to establish its validity and reliability (Sperling et al., 2023). The findings from this study will inform evidence about the utility of online, remote neuropsychological assessment of SCD and whether SCD recruited from the community may show subtle cognitive impairment using this assessment method.

Chapter Four provides a critical discussion of the findings, including strengths and limitations, theoretical and clinical implications, and recommendations for future research.

Chapter Two is a systematic review and meta-analysis which was written up in preparation for submission to Neuropsychology Review (see Appendix A for author guidelines). The following supporting documents for this chapter are provided in the appendix: the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool which was adapted to assess risk of bias for the studies included in the review (Appendix B).

Chapter Three is an empirical study which was written up in preparation for submission to PloS Digital Health (see Appendix C for author guidelines). The following supporting documents for this chapter are provided in the appendix: a statement of ethical approval for the study (Appendix D), the Participant Information Sheet used during recruitment (Appendix E), the Consent Form for the study (Appendix F), and questionnaires used during data collection to assess subjective cognitive decline (the Cognitive Change Index; Appendix G), depression (the Geriatric Depression Scale; Appendix H), and anxiety (the Geriatric Anxiety Inventory; Appendix I).

CHAPTER TWO: Systematic review

Memory test performance of people with subjective cognitive decline recruited from different settings: A systematic review and meta-analysis

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Abstract

Subjective cognitive decline (SCD) is defined as self-experienced cognitive decline without objective impairment on standardised tests. Research suggests SCD may be associated with subtle impairment on detailed neuropsychological assessment and might therefore indicate the earliest stage of neurodegeneration. This review (PROSPERO: CRD42023382096) seeks to determine whether group differences in memory task performance between people with and without SCD exist. The review included studies since 2014 comparing episodic memory performance between people with and without SCD; where people with SCD were recruited exclusively from community or medical settings. Studies providing data for people with mild cognitive impairment (MCI) were included in a separate meta-analysis comparing SCD and MCI. A systematic search was conducted (PsycINFO, Web of Science, MEDLINE, CINAHL, and PubMed on 11th August 2023). Risk of bias was assessed using the Quality Assessment of Diagnostic Accuracy Studies tool. 1,815 records were identified, of which 45 met inclusion criteria and were included in a random-effects meta-analysis (SCD N=5,949, Non-SCD N=8,470). Twenty-one studies additionally provided data for an MCI group (SCD N=1,035, MCI N=2,119). Results indicated people with SCD performed significantly worse than people without SCD (Hedges' *g*=-0.24, 95% CI=-0.43, -0.04) and significantly better than MCI participants (Hedges' *g*=1.53, 95% CI=0.95, 2.11). For both meta-analyses there was significant between-study heterogeneity and no moderating effect of recruitment source. There was a significant risk of publication bias for the meta-analysis comparing SCD to MCI. These results suggest detailed memory assessment may be sensitive to SCD. SCD may represent the emergence of objective memory decline due to neurodegeneration.

Introduction

Dementia presents a considerable global challenge, with rising prevalence projected to place a significant burden on healthcare and society in the coming decades, making dementia prevention and treatment a key priority for healthcare research (Shah et al., 2016). Treatment studies have been hampered by the lack of methods for identifying the earliest stages of the disease where people are most likely to benefit from disease-modifying interventions (Elmaleh et al., 2019; Rossini et al., 2020). Evidence suggests that the pathological processes of neurodegeneration begin years before the onset of symptoms (Rohrer et al., 2015; Tondelli et al., 2012; Venneri & De Marco, 2020). Subsequently, there is considerable research interest in the early, pre-diagnostic, or prodromal, detection of neurodegenerative disease to target prevention strategies and clinical trials of potential treatments (Azevedo et al., 2023; Coughlan et al., 2018; Swaddiwudhipong et al., 2023).

The self-experience of cognitive decline ("subjective cognitive decline"; SCD) has been suggested as one such potential indicator of early dementia (Studart & Nitrini, 2016). In 2014, a group of researchers developed a framework to define SCD for research purposes (Jessen, Amariglio, et al., 2014). In it, they define SCD as "self-experienced persistent decline in cognitive capacity in comparison with a previously normal status and unrelated to an acute event" in the context of "normal age-, gender-, and education-adjusted performance on standardised cognitive tests, which are used to classify mild cognitive impairment (MCI) or prodromal Alzheimer's disease". Estimated prevalence rates of SCD vary widely due to methodological heterogeneity between studies, including differences in the definition used for SCD, however it may be as high as 25-56% in adults aged 65+ (Garcia-Ptacek et al., 2016; Jonker et al., 1999). There are reports that the number of people seeking medical advice for SCD is growing (Jessen et al., 2020), perhaps due to an ageing population or increased awareness of dementia. While most people who experience SCD do not go on to

develop MCI or dementia, evidence from meta-analyses of longitudinal studies estimate that they may be at double the risk of doing so compared to people without SCD (Mitchell et al., 2014; Pike et al., 2022). Mitchell et al. (2014) reported that approximately 6.6% of people with SCD will progress to MCI and 2.3% to dementia per year. Further, there is evidence for brain structural and functional changes in people with SCD, supporting the hypothesis that SCD can represent an early stage of neurodegeneration (Chao et al., 2022; Erk et al., 2011; Jessen et al., 2006; Saykin et al., 2006).

Although SCD is defined by an absence of objective impairment on standardised cognitive tests, there is evidence for subtle impairment using detailed neuropsychological assessment (Koppara et al., 2015; Lazarou et al., 2021; Macoir et al., 2019; Zlatar et al., 2022). Most diagnostic screening tests are subject to ceiling effects and therefore may not be sensitive to SCD (Hoops et al., 2009). Furthermore, in a study of healthy people from the UK Biobank, Azevedo et al. (2023) used machine learning to identify a cohort of people who have an Alzheimer's disease-like neuroimaging profile which may indicate the earliest stages of the disease. These same people showed subtle neuropsychological impairment, including in memory ability. It is unclear whether these people had a subjective experience of cognitive decline, however, the findings add support to the suggestion that a pre-MCI stage of neurodegenerative disease may be associated with subtle cognitive changes. An important objective for research will be to identify tests which are sensitive to these subtle changes, to begin to establish a "cognitive profile" of SCD which may indicate greater risk of later dementia, and so that concerns about SCD can be explored clinically (Lazarou et al., 2021; Macoir et al., 2019).

A key question to explore is whether potential subtle differences in cognitive ability between people with and without SCD are driven by those who are concerned about their SCD, and therefore reflects the suggestion that help-seeking is associated with increased risk

of dementia in SCD or MCI (Espenes et al., 2020; Molinuevo et al., 2017; Zhao et al., 2021). This can be explored by considering the recruitment source of people with SCD, i.e. whether they were recruited from the community or via a healthcare setting. For example, many of the studies reporting group differences in neuropsychological test scores recruited people with SCD from a memory clinic or other healthcare setting (Koppara et al., 2015; Lazarou et al., 2021; Macoir et al., 2019; Wolfsgruber et al., 2020). People with SCD who are seeking help may differ from those who are not seeking help in ways that may contribute to their risk of dementia (e.g. family history, degree of perceived change in cognitive ability, education; Pike et al., 2022), therefore it is important for research to consider the impact of recruitment source in investigations of SCD (Espenes et al., 2020; Molinuevo et al., 2017; Zhao et al., 2021). Indeed, in their meta-analysis, Pike et al. (2022) found evidence that people with SCD recruited via a medical setting had an increased risk of progression to dementia, although the risk was still elevated in those recruited from a community sample. Presentation at a memory clinic is among the "SCD plus criteria" factors associated with increased risk of cognitive decline in people with SCD (along with subjective decline in memory, onset of SCD within the last five years, onset at age 60+, persistence of SCD, and informant-reported cognitive decline) (Jessen et al., 2020; Slot et al., 2019).

Since SCD has had operationalised criteria for 10 years, a significant body of research has emerged. This means that it is possible to conduct a meta-analysis to further our understanding of SCD. The aim of the present review was to synthesise the literature reporting detailed memory task performance by people with SCD and without SCD to test the hypothesis that, on average, people with SCD show subtle impairment on detailed memory assessment, and therefore, detailed memory assessment may be sensitive to SCD. We focussed on episodic memory performance since memory is considered to be one of the most likely domains affected in preclinical Alzheimer's disease (Jessen, Wolfsgruber, et al., 2014)

and episodic memory appears to be the domain most commonly used in the characterisation of SCD (Pike et al., 2022). A second aim was to investigate whether recruitment source (community versus clinic-based, i.e. help-seekers) moderates a potential effect of group on memory task performance, in order to explore factors which may be associated with an increased risk of objective cognitive decline in SCD. Therefore, we limited our search to studies where people with SCD were recruited exclusively from the community or from a healthcare setting. In line with previous findings in SCD and MCI, we hypothesised that people with SCD recruited from a healthcare setting would show greater risk of impairment in memory performance.

Methods

Study registration

The current study was pre-registered on the International Prospective Register of Systematic Reviews (PROSPERO; Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023382096) on 10th January 2023, and followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Page et al., 2021) (see Appendix 2A for PRISMA checklists).

Search strategy

A systematic search of the literature was conducted by the primary researcher (KAP) on 11th August 2023 to identify all studies reporting memory task performance by people with SCD where SCD participants were recruited exclusively from either a community or a medical setting, and published since 2014 to ensure studies included people who experience SCD as operationalised by the SCD-Initiative (Jessen, Amariglio, et al., 2014). The following

databases were searched: PsycINFO, Web of Science, MEDLINE, CINAHL, and PubMed. ScienceDirect was not included in the search as the website does not support the use of wildcards. Grey literature was not included due to SCD being a relatively new concept. The search terms were as follows: “subjective cognitive decline” AND neuropsychologic* SINCE 2014. The initial search was open to all studies where people with SCD completed neuropsychological tests, to ensure the inclusion of studies which incorporated memory assessment but did not explicitly identify the use of memory tasks within the abstract.

Study selection

After removal of duplicates, titles and abstracts of papers retrieved during the initial search were screened by two researchers independently (KAP and FE) for inclusion and exclusion criteria. Disagreements were dealt with by discussion. The PRISMA flow chart (Figure 2.1) for the review shows reasons for exclusions. Studies were included in the full text screen if people with SCD completed any neuropsychological tests, even if it was only suggested in the abstract e.g. “X correlated with memory performance”. The primary researcher (KAP) then screened full texts.

Studies were included in the review if they met the following criteria: (1) peer-reviewed published papers since 2014, (2) in which people with SCD completed validated episodic memory tasks and performance was compared to a group without SCD (Non-SCD), as a minimum; (3) the studies reported raw test scores for each group (e.g. means and standard deviations, z-scores); and (4) people with SCD were recruited exclusively from the community (e.g. local advertisement, population based studies) or from a medical setting (e.g. memory clinic, referral from a clinician), in order to investigate the influence of recruitment source. We excluded studies where SCD participants were recruited from a mixture of community and medical settings.

As previously described, we focused on episodic memory, therefore, we did not include tasks measuring other aspects of memory, such as prospective memory or working memory, which rely on involvement of other cognitive abilities in addition to memory, such as executive functioning (Martin et al., 2003). We included studies using validated episodic memory tasks only (i.e. those with published psychometric properties) commonly used in neuropsychological assessments – experimental memory tasks were excluded.

Where different studies recruited participants from the same centre, the methods were inspected in detail by KAP, AL and MH for evidence of potential participant overlap. Where there was suspicion of overlapping samples, the study with the largest sample size was included, regardless of number and type of memory tasks used.

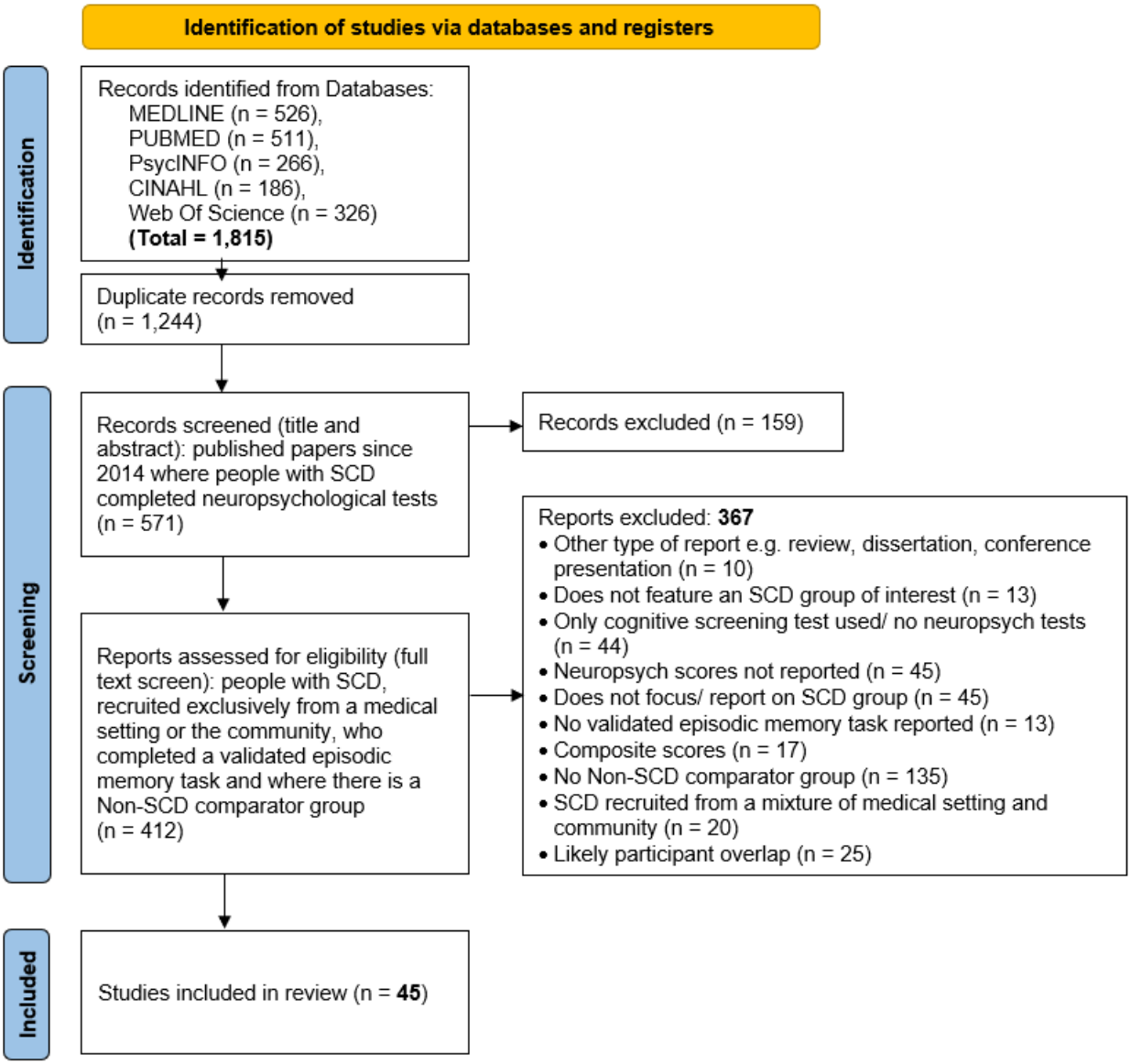

Fig. 2.1 PRISMA flow chart for review

Data extraction

The following data were extracted from each study by the primary researcher (KAP): (1) study details (author, publication year, study title), (2) groups (e.g. SCD, Non-SCD, MCI) and sample sizes, (3) demographic information for each group (age, sex, years of education, ethnicity, Mini-Mental State Examination score; Cockrell & Folstein, 2002), (4) criteria and/or method for defining SCD, (5) recruitment source of SCD group, (6) memory tests used (including which subscores were reported, where stated), (7) raw memory test scores (e.g.

means and SDs, medians, z scores) or effect sizes. Where recruitment source was not specified authors were contacted for clarification.

Data synthesis and analysis

Effect sizes (standardised mean difference [SMD], Hedges' *g*; Hedges, 1981) were calculated for differences in memory test scores between (1) SCD and Non-SCD participants, and (2) SCD and MCI participants, where MCI data were available. Separate syntheses were performed to compare SCD with Non-SCD or MCI, each using random effects models to calculate an overall effect size across studies. The direction of the effect was negative if SCD participants performed worse than Non-SCD participants or MCI participants. Risk of publication bias was assessed using Egger's regression test (Egger et al., 1997) and Duval and Tweedie's (2000) trim and fill method. Heterogeneity of effect sizes was assessed using the Q statistic (with a significant Q statistic at the level of $p < 0.05$ indicating significant heterogeneity; Higgins & Thompson, 2002). Recruitment source (community, medical centre) was entered as a covariate in moderator analyses for both meta-analyses.

Where studies provided data for multiple MCI groups, separately, (e.g. "amnestic" and "nonamnestic" MCI, or "early" and "late" MCI) the groups were combined into one "MCI" group for the present analysis. Ribaldi et al. (2022) reported data for two SCD subgroups, separately. These were combined into one SCD group. Similarly, where "SCD" and "SCD plus" groups were reported separately, these were combined into a single SCD group (see Table 2.1) as it is highly likely that for studies featuring an SCD group only, the SCD group would include a mixture of people who do and do not meet the additional SCD plus criteria. Groups were combined by decomposing the means and SDs using an online tool: https://www.statstodo.com/CombineMeansSDs.php. Two studies (Hao et al., 2020;

Yang et al., 2022; Table 2.1) included only an ‘SCD plus’ group, therefore, these were included as SCD in the present analyses.

For studies reporting multiple memory task sub-measures, (e.g. an immediate and a delayed recall subscore) or multiple memory tests, the effects sizes (Cohen’s *d*) were averaged across the tasks or sub-measures and entered into the analysis of overall effect size. Where Cohen’s *d* was not reported by individual studies, it was calculated from pooled SDs using the following formula (Cohen, 2013):

$$SD*_{pooled} = \sqrt{\frac{(n_1 - 1)SD_1^2 + (n_2 - 1)SD_2^2}{n_1 + n_2 - 2}}$$

In one study (Luck et al., 2018), a subsample of the participants completed the memory tasks. Luck et al. did not report demographic information or group sizes (SCD, Non-SCD) for the reduced sample. Therefore, in order to include this study in the meta-analysis, the prevalence of SCD in the subsample was assumed to be equivalent to that of the full sample (reported as 53%) and Cohen’s *d* was calculated using the assumed group sizes of 1,461 for SCD and 1,295 for Non-SCD. Snitz et al. (2015) presented data for each participant individually, therefore, means and SDs were calculated to include in the meta-analysis.

Two studies (Morrison et al., 2023; Papadatos & Phillips, 2023) recruited SCD participants from large database studies (Alzheimer's Disease Neuroimaging Initiative and the Comprehensive Assessment of Neurodegeneration and Dementia Study). Efforts were made to establish whether the SCD groups in these databases were recruited from community or healthcare settings by contacting authors. It was not possible to establish a definitive recruitment source for all SCD participants from these databases. Therefore, in order to include these studies within the overall meta-analyses, the recruitment was coded as ‘database’ rather than community or clinic-based, for the purpose of the moderator analyses. Other studies which used databases to recruit SCD participants whereby it was possible to

establish recruitment source were included as community, clinic-based, or excluded (if a mixture), as appropriate. Any study in which it was clear that the SCD group contained a mixture of people recruited via community and clinic-based sources were excluded.

Data were analysed using the "metafor" package (version 4.4-0) (Viechtbauer, 2010) with R (version 4.0.2) and RStudio (version 2023.06.1).

Study quality

Risk of bias was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool (Whiting et al., 2011). We used the version developed by Pike et al. (2022) in their review of risk for MCI or dementia in SCD. We further adapted their version to reflect the content of our review. The QUADAS-2 is structured to assess risk of bias across four domains: patient selection, index test (SCD), reference standard (memory assessment), and patient flow and timing. For each domain, if any signalling questions were answered negatively that domain was rated as having high risk of bias. The study quality ratings were used to provide a summary of the potential impact of bias across studies included in the review.

Results

Forty-five studies provided data comparing memory task performance in people with SCD to people without SCD and were included in the meta-analysis (Table 2.1). Twenty-one of these also provided data for an MCI group, and therefore were included in a separate meta-analysis of SCD versus MCI. A range of methods were used to define SCD across the studies, as shown in Table 2.2.

Table 2.1 The characteristics of the studies included in the meta-analysis

Study	Groups (N)	Age M (SD)	Sex (% F)	Education, years M (SD)	Ethnicity (% non-white)	MMSE M (SD)	Source of SCD group	Memory tests used (subscores)
1) (Ali et al., 2022)	SCD (33); Non-SCD (26); MCI (24)	72.7 (5.25); 71.9 (5.09); 71.0 (6.42)	54.5; 42.3; 50.0	13.2 (2.35); 12.9 (2.52); 11.8 (2.94)	N.R.	27.0 (1.95); 28.3 (1.61); 26.6 (1.74)	Community	AVLT (delayed recall and recognition)
2) (Ávila-Villanueva et al., 2018)	SCD (851)†; Non-SCD (240)	74.78 (3.88); 74.48 (3.84)	63.9; 64.6	10.40 (5.74); 11.56 (5.81)	N.R.	N/A	Community	FCSRT (free immediate, total immediate, free delayed, total delayed)
3) (Boccardi et al., 2021)	SCD (44); Non-SCD (87); MCI (78)	79.45 (5.38); 79.56 (6.28); 79.63 (7.03)	70.5; 63.2; 60.0	7.32 (4.35); 7.62 (4.30); 7.54 (5.17)	N.R.	27.95 (2.21); 28.47 (1.20); 27.21 (2.39)	Clinic-based	Babcock story recall, RAVLT (immediate and delayed recall)
4) (Caselli et al., 2014)	SCD (137); Non-SCD (310)	59.8 (8.3); 58.7 (6.9)	68.1; 70.8	15.5 (2.6); 15.7 (2.4)	N.R.	29.4 (0.8); 29.7 (0.6)	Community (with family history of dementia)	AVLT (delayed recall), Benton Visual Retention test, FCSRT (total free recall), ROCF (absolute recall), WMS (paragraph delayed recall)

5) (Chen et al., 2021)	SCD (32); Non-SCD (33)	65.22 (5.02); 64.55 (5.33)	84.4; 75.8	12.25 (2.62); 12.97 (3.34)	N.R.	28.66 (1.31); 28.97 (1.31)	Community	AVLT (immediate, short delayed, long delayed, cued recall, recognition)
6) (Chi et al., 2021)	SCD (84); Non-SCD (120); MCI (56)	81.56 (5.18); 80.28 (5.53); 80.79 (6.12)	64.3; 66.7; 75.0	15.10 (3.20); 14.99 (3.13); 12.39 (3.53)	28.6; 37.5; 62.5	N/A	Community	BVMT
7) (De Simone et al., 2023)	SCD (18); Non-SCD (15)	69.4 (7.8); 69.2 (8.1)	72.2; 40.0	13.2 (3.8); 13.5 (1.2)	N.R.	27.9 (1.6); 28.3 (2.0)	Clinic-based	15-word list test (immediate and delayed recall, recognition), ROCF (immediate and delayed recall), short story test (immediate and delayed recall)

8) (Dillen et al., 2017)	SCD (28); Non-SCD (25)	65.8 (7.8); 62.4 (7.0)	53.6; 40.0	13.6 (4.2); 15.2 (3.9)	N.R.	28.9 (1.8); 29.2 (1.3)	Clinic-based	RAVLT (total learning, delayed recall), WMS logical memory (total learning, delayed recall), WMS design memory (total learning, delayed recall)
9) (Esmaeili et al., 2022)	SCD (17); Non-SCD (15); MCI (30)	65.35 (7.7); 65.33 (4.04); 67.90 (7.6)	64.7; 53.3; 76.7	9.8 (3.1); 9.4 (2.4); 9.4 (3.3)	N.R.	28.29 (1.35); 28.46 (1.30); 25.53 (3.21)	Community	RAVLT
10) (Fan et al., 2018)	SCD (43); Non-SCD (34); MCI (44)	66.1 (7.0); 67.8 (7.4); 73.9 (8.0)	51.2; 73.5; 59.1	13.6 (2.9); 13.0 (4.3); 12.6 (3.5)	N.R.	28.9 (1.0); 28.6 (1.2); 26.1 (3.0)	Clinic-based	WMS logical memory (immediate and delayed recall), WMS family picture (immediate and delayed recall)
11) (Fu et al., 2022)	SCD (35); Non-SCD (42)	64.54 (7.29); 64.24 (6.16)	57.1; 64.3	11.83 (3.67); 11.17 (5.61)	100.0 (Chinese Han, whole sample)	N/A	Clinic-based	AVLT (immediate recall, delayed recall, recognition)

12) (Hao et al., 2020)	SCD plus (517); Non-SCD (84)	N.R.	N.R.	N.R.	100.0 (Chinese Han, whole sample)	N.R.	Community	AVLT (delayed recall)
13) (He et al., 2023)	SCD (62); Non-SCD (35)	67 (65, 71)*; 69 (65, 71.5)*	66.1; 68.6	15 (12, 16)*; 14 (12, 16)*	N.R.	28.03 (2.14); 28.77 (1.48)	Clinic-based	AVLT (long-delayed recall, recognition)
14) (Hong et al., 2014)	SCD (47); Non-SCD (23)	62.3 (8.5); 66.4 (6.9)	76.6; 78.3	11.8 (4.4); 12.4 (4.3)	N.R.	28.8 (1.0); 28.6 (1.0)	Clinic-based	ROCF (delayed recall), SVLT (delayed recall)
15) (Koppara et al., 2015)	SCD (19); Non-SCD (23); MCI (23)	66.79 (7.58); 68.00 (8.31); 72.82 (4.37)	42; 39; 55	16.53 (3.03); 14.39 (3.07); 13.27 (2.96)	N.R.	29.16 (1.17); 29.04 (1.07); 26.55 (2.34)	Clinic-based	CERAD word list (immediate recall, delayed recall), CERAD visual recall
16) (Lazarou et al., 2020)	SCD (20); Non-SCD (22); MCI (30)	64.90 (7.92); 67.22 (4.03); 70.40 (5.96)	65; 63.6; 73.3	13.75 (3.29); 13.16 (4.59); 11.45 (4.06)	N.R.	29.25 (1.06); 29.13 (0.99); 27.13 (2.55)	Clinic-based	RAVLT (1, 2, total score, 4), ROCF (delayed recall), Rivermead behavioural memory test (immediate and delayed recall)

17) (Lazarou et al., 2021)	SCD (78); Non-SCD (65); MCI (89)	66.50 (9.15); 62.94 (7.60); 70.96 (7.87)	N.R.	14.76 (4.18); 14.77 (2.99); 14.33 (2.55)	N.R.	28.50 (0.89); 29.42 (0.71); 26.54 (1.57)	Clinic-based	M@T (total score)
18) (Lee et al., 2023)	SCD (62); Non-SCD (65); MCI (25)	73.7 (3.6); 73.0 (4.2); 72.0 (5.5)	67.7; 69.2; 72.0	9.5 (4.2); 10.5 (4.7); 10.8 (4.7)	N.R.	27.0 (1.9); 26.7 (2.3); 25.7 (3.7)	Community	SVLT (delayed recall, recognition)
19) (Li et al., 2022)	SCD (94); Non-SCD (64)	67.07 (5.57); 67.59 (6.42)	60.6; 45.3	8.67 (3.43); 8.95 (3.87)	100.0 (Chinese Han, whole sample)	27.70 (2.20); 28.14 (1.74)	Community	AVLT
20) (López-Higes et al., 2017)	SCD (66); Non-SCD (69)	70.62 (4.86); 70.42 (4.52)	77.3; 63.8	13.16 (5.76); 13.88 (5.69)	N.R.	28.86 (1.02); 29.00 (1.08)	Clinic-based	WMS logical memory (delayed recall)
21) (Luck et al., 2018)	SCD and Non-SCD (total N = 2756)	N.R.	N.R.	N.R.	N.R.	N.R.	Community	CERAD (word list learning, recall and recognition)
22) (Macoir et al., 2019)	SCD (20); Non-SCD (20); MCI (20)	66.4 (6.0); 70.8 (7.1); 71.1 (6.1)	80; 70: 55	16.2 (2.25); 14.9 (2.95); 13.45 (3.3)	N.R.	N/A	Clinic-based	RL/RI (free recall 1, 2, 3)
23) (Markova et al., 2019)	SCD (85); Non-SCD (82); MCI (57)	69.2 (6.7); 69.4 (5.9); 73.6 (5.9)	68.2; 65.9; 50.9	14.7 (2.7); 14.4 (2.9); 13.7 (3.2)	N.R.	28.9 (1.1); 28.6 (1.2); 27.1 (1.5)	Clinic-based	RAVLT (total recall, delayed recall)

24) (Morrison et al., 2023)	SCD (103); Non-SCD (390)	72.40 (5.52); 74.84 (5.73)	58; 51	16.77 (2.56); 16.22 (2.75)	N.R.	N/A	Database	RAVLT (immediate recall, percent forgetting)
25) (Moulinet et al., 2022)	SCD (35); Non-SCD (56)	67.51 (6.85); 69.75 (5.61)	48.6; 55.4	13.43 (3.11); 12.64 (3.82)	N.R.	28.88 (1.05); 29.00 (1.08)	Clinic-based	ESR word list (immediate and delayed summed)
26) (Papadatos & Phillips, 2023)	SCD (55); Non-SCD (55); MCI (101)	70.08 (7.00); 69.07 (5.56); 71.37 (6.41)	78.2; 81.8; 44.6	16.97 (3.10); 15.77 (3.24); 15.73 (4.06)	N.R.	N/A	Database	BVMT (total recall), RAVLT (total recall)
27) (Peng et al., 2023)	SCD (89); Non-SCD (285); MCI (720)	64.6 (9.0); 67.6 (9.4); 74.0 (9.1)	64.0; 61.4; 51.7	13.9 (3.1); 13.5 (3.2); 10.8 (4.8)	N.R.	28.7 (1.1); 29.0 (1.1); 26.5 (2.5)	Clinic-based	CFT (delayed recall), CVLT (total score), Story recall - Chinese version
28) (Polcher et al., 2017)	SCD (18); Non-SCD (13); MCI (15)	66.40 (7.89); 70.69 (9.17); 63.67 (8.89)	38.9; 53.8; 46.7	15.28 (2.56); 14.54 (2.63); 14.47 (2.88)	N.R.	N.R.	Clinic-based	CANTAB-PAL (total errors adjusted, six shapes total error adjusted, stages completed)
29) (Pusswald et al., 2016)	SCD (110); Non-SCD (317); MCI (521)	65 (59, 72)*; 66 (60, 72)*; N/A	52.7; 47.0; 59.7	12 (8, 15)*; 11 (8, 15)*; N/A	N.R.	29 (28, 29)*; 29 (28, 29)*; N/A	Clinic-based	VSRT (total recall, immediate recall, delayed recall, recognition)

30) (Ren et al., 2023)	SCD (46); Non-SCD (56)	64.3 (6.5); 61.9 (8.9)	71.7; 66.1	12.2 (3.2); 12.7 (3.4)	100.0 (Chinese, whole sample)	28.4 (1.5); 28.8 (1.0)	Community	AVLT (delayed recall, recognition)
31) (Ribaldi et al., 2022)	SCD (370); Non-SCD (586)	72.2 (1.2); 72.0 (1.3)	55; 53	7.3 (3.3); 7.1 (3.3)	N.R.	27.4 (1.8); 27.3 (1.9)	Community	RAVLT (immediate recall, delayed recall), ROCF (recall), logical memory
32) (Ruiz-Rizzo et al., 2022)	SCD (16); Non-SCD (21)	69.2 (7.8); 70.7 (7.9)	93.8; 71.4	N.R.	75.0; 95.2	28.9 (1.0); 28.4 (1.5)	Community	RAVLT (total and retention score), WMS (auditory memory index, visual memory index, delayed memory index, immediate memory index)
33) (Sánchez-Benavides et al., 2018)	SCD (572)[†]; Non-SCD (2098)	57.16 (6.85); 55.41 (6.62)	65.0; 62.7	13.14 (3.50); 13.41 (3.52)	N.R.	N.R.	Community	MBT (total paired recall, total free recall, total delayed free recall, total delayed paired recall)

34) (Schmicker et al., 2023)	SCD (17)†; Non-SCD (18)	71.7 (7.0); 73.5 (4.8)	47.1; 55.6	13.8 (2.7); 14.3 (2.2)	N.R.	28.1 (1.5); 29.1 (1.0)	Clinic-based	CERAD word list (delayed recall) and figure delayed recall
35) (Smart & Krawitz, 2015)	SCD (17); Non-SCD (25)	69.47 (3.38); 69.88 (3.36)	70.6; 40.0	16.53 (2.55); 16.92 (4.07)	5.0 (whole sample)	N.R.	Community	ROCF (immediate recall, delayed recall, recognition), WMS logical memory (immediate recall, delayed recall, recognition)
36) (Snitz et al., 2015)	SCD (14); Non-SCD (84)	68.1 (4.0); 73.6 (5.8)	64.3; 64.3	17.6 (2.1); 15.1 (2.6)	N.R.	29.1 (1.0); 28.6 (1.3)	Clinic-based	CERAD word list (delayed recall, completed by N=13 SCD), Memory Capacity Test (immediate cued recall x2 lists, immediate free recall x2 lists, completed by N=68 Non-SCD)

37) (Sun et al., 2019)	SCD (65); Non-SCD (73)	65.85 (4.85); 64.55 (5.52)	64.6; 47.9	11.86 (2.70); 11.68 (3.31)	100.0 (Chinese Han; whole sample)	28.65 (1.23); 28.79 (1.38)	Clinic-based	AVLT (immediate recall, delayed recall, recognition)
38) (Tsai et al., 2021)	SCD (39); Non-SCD (96); MCI (40)	66.97 (6.10); 65.10 (5.28); 65.92 (6.07)	71.8; 81.3; 72.5	12.77 (3.62); 13.42 (3.02); 11.25 (3.66)	N.R.	28.72 (1.45); 28.95 (1.09); 27.95 (1.41)	Community	CVLT (immediate recall, short-delay recall, long-delay recall, cued recall, recognition)
39) (Vogel et al., 2022)	SCD (17); Non-SCD (30); MCI (17)	63.1 (7.0); 68.5 (7.6); 71.9 (5.2)	70.6; 46.7; 58.8	N.R.	(ethnic Danes, whole sample)	30 (28-30)**; 30 (26-30)**; 28 (25-30)**	Clinic-based	LASSI-L (all free, cued and delayed recall components)
40) (Wang et al., 2021)	SCD (84); Non-SCD (35); MCI (129)	67.0 (5.6); 67.5 (5.3); 67.8 (8.6)	61.9; 48.6; 68.2	11.5 (3.3); 11.8 (2.9); 9.8 (3.2)	N.R.	26.8 (2.0); 27.0 (1.5); 24.9 (3.0)	Clinic-based	AVLT (immediate recall, short delayed recall, long delayed recall, recognition)
41) (Yang et al., 2022)	SCD plus (32); Non-SCD (41); MCI (33)	68.06 (8.02); 67.06 (6.07); 68.64 (5.87)	59.4; 51.5; 75.8	9.85 (1.75); 10.08 (1.63); 9.91 (1.58)	N.R.	26.23 (2.46); 27.08 (1.76); 24.29 (2.52)	Clinic-based	AVLT (immediate recall, delayed recall, recognition)

42) (Yu et al., 2020)	SCD (60); Non-SCD (55); MCI (40)	70.84 (7.38); 71.04 (5.25); 73.15 (7.08)	53.3; 49.1; 47.5	11.55 (2.57); 10.31 (4.05); 9.05 (3.31)	100.0 (Chinese, whole sample)	28.69 (1.49); 29.13 (2.04); 28.03 (2.48)	Clinic-based	RAVLT
43) (Zheng et al., 2023)	SCD (25); Non-SCD (28)	67.52 (4.40); 66.29 (3.73)	60.0; 35.7	10.92 (2.12); 11.93 (2.48)	N.R.	N/A	Community	AVLT (total learning, delayed recall)
44) (Zhu et al., 2021)	SCD (26); Non-SCD (33); MCI (27)	64.70 (4.20); 66.85 (7.15); 68.80 (9.33)	69.2; 48.5; 48.1	11.75 (3.53); 12.02 (3.32); 11.68 (3.71)	100.0, (Chinese Han; whole sample)	28.21 (1.47); 28.57 (1.63); 26.76 (2.34)	Community	AVLT (immediate recall, delayed recall, recognition)
45) (Zullo et al., 2021)	SCD (286); Non-SCD (1281)	71.17; 70.81	57.69; 58.86	N.R.	N.R.	N/A	Community	DMT (identification, immediate recall, differed free recall, differed cued recall, recognition, free recall sum of series, cued recall sum of series)

Note: AVLT = Auditory Verbal Learning Test, BVMT = Brief Visuospatial Memory Test, CANTAB-PAL = Cambridge Neuropsychological Test Automated Battery-Paired Associates Learning, CERAD = Consortium to Establish a Registry for Alzheimer's Disease, CFT = Complex Figure Test, CVLT = California Verbal Learning Test, DMT = Double Memory Test, ESR = Encoding, Storage and Recuperation, FCSRT = Free and Cued Selective Reminding Test, LASSI-L = The Loewenstein-Acevedo Scales for Semantic Interference and Learning, MBT = Memory Binding Test, MCI = mild cognitive impairment, M@T = Memory Alteration Test, MMSE = Mini-Mental State Examination, Non-SCD = people without subjective cognitive decline, N.R. = not reported, RAVLT = Rey Auditory Verbal Learning Test, RL/RI = 16-item free and cued recall, ROCF = Rey Complex Figure Test, SCD = subjective cognitive decline, SVLT = Seoul Verbal Learning Test, VSRT = verbal selective reminding test, WMS = Wechsler Memory Scale. *Median (IQR), **Median (range), †SCD and SCD plus groups combined.

Table 2.2 Criteria for defining SCD across the studies included in the meta-analysis

Study	Criteria
1. (Ali et al., 2022)	**Guidelines cited:** (Cullen et al., 2019; Slot et al., 2019). (1) Self-reported persistent decline in the memory domain of cognition for more than 6 months; (2) concerns about memory loss and feeling of deteriorating performance compared to individuals of the same age group; (3) worse performance on standard cognitive tests adjusted for age, gender, and education; and (4) did not meet MCI or dementia diagnostic criteria.
2. (Ávila-Villanueva et al., 2018)	**Guidelines cited:** (Jessen, Amariglio, et al., 2014). The primary measure for SCD was the SCD scale. Scores 0-1 on the SCD scale was considered as non-indicative of SCD while scores ranging 4–12 were conceived as a strong signal of SCD. Intermediate 2-3 scores were thought to be at borderline and in those cases, the information from 9 yes/no-type questions was taken into account as a secondary measure to classify the participants.
3. (Boccardi et al., 2021)	**Guidelines cited:** (Jessen, Amariglio, et al., 2014). Normal age, gender, and education-adjusted performance on standardised cognitive tests; self-experienced persistent decline in cognitive capacity in comparison with a previously normal status and unrelated to an acute event. Criteria must be present and not explained by a psychiatric or neurologic disease medical disorder, medication, or substance use.
4. (Caselli et al., 2014)	**Guidelines cited:** N/A. All participants and their informants (typically a spouse) completed the paired Multidimensional Assessment of Neurodegenerative Symptoms questionnaire (MANS) (Locke et al., 2009). The MANS are paired self-and informant-based questionnaires composed of 87 questions that assess changes over the preceding year in daily habits, personality, and motor functioning. Any score greater than zero was considered “positive” for endorsed decline on the MANS-self.
5. (Chen et al., 2021)	**Guidelines cited:** N/A. Subjects with memory complaints within the last 5 years and expressed worries associated with memory decline were assigned to the SCD group; those without memory complaints and cognitive impairments were recruited as [Non-SCD]s.

6. (Chi et al., 2021)	**Guidelines cited:** N/A. SCD was classified in cognitively intact participants (i.e., cognitive factor Z scores for all three domains did not fall >1 SD below the mean of the robust sample) who also exceeded an optimal cut point for self- and/or informant concerns using the Cognitive Change Index (Rattanabannakit et al., 2016).
7. (De Simone et al., 2023)	**Guidelines cited:** (Jessen, Amariglio, et al., 2014). Concern over a self-experienced memory decline, operationalised with the following procedure: We first asked participants "Do you feel like your memory has become worse?" (possible answers: yes/no). In case of a positive response we asked whether memory decline was experienced as worrisome by asking "Does this worry you?" (possible answers: yes/no). SCD was defined by endorsement of perceived decline with concern about memory decline.
8. (Dillen et al., 2017)	**Guidelines cited:** (Jessen, Amariglio, et al., 2014). Inclusion criteria for SCD participants consisted of self-perceived memory complaints with a cut-off value of ≥25 on the memory complaint questionnaire (MAC-Q) (Crook et al., 2000) but average scores on neuropsychological tests (corrected for age, gender, and education).
9. (Esmaeili et al., 2022)	**Guidelines cited:** (Jessen, Wolfsgruber, et al., 2014). Since at the time of the study there were no standard criteria or questionnaires in Persian for the diagnosis of SCD, according to the previous studies, participants were asked, "Do you feel like your memory is becoming worse?" and if so, "Did that worry you?". If they answered 'yes' to both questions, they would meet the initial criteria for SCD.
10. (Fan et al., 2018)	**Guidelines cited:** (Molinuevo et al., 2017). Subjects with cognitive decline complaints but normal neuropsychological performance (better than −1.5 SD of their age- and education-matched norm) were categorised as the SCD group.

11.(Fu et al., 2022)	**Guidelines cited:** (Jessen, Amariglio, et al., 2014). (1) Self-experienced memory decline, rather than other domains of cognition and last within five years; (2) feeling of worse performance than others of the same age group; (3) the Montreal Cognitive Assessment, Beijing version, (Lu et al., 2011) score was in the normal range; (4) only one of the two memory tests (AVLT-delayed and AVLT-recall) was abnormal (decline one Standard Deviation (SD) compared with Non-SCD); and (5) the CDR score was 0; (6) patients diagnosed with aMCI, AD, or other types of dementia were excluded.
12.(Hao et al., 2020)	**Guidelines cited:** (Jessen, Amariglio, et al., 2014). For SCD (plus), all the following criterion needed to be met: (1) participants reported the problem in memory; (2) age of onset ≥ 60 years old; (3) achieved a normal score in all four cognitive domains and Montreal Cognitive Assessment-Basic; (4) ADL was normal; (5) Hachinski Ischemic Scale (Hachinski et al., 1975) score < 4.
13.(He et al., 2023)	**Guidelines cited:** (Jessen et al., 2020; Jessen, Amariglio, et al., 2014). (1) self-experienced, persistent cognitive decline, mainly in the memory domain but not in other cognitive domains, which was not related to the acute event; (2) the onset was within 5 years; (3) issues associated with SCD; (4) the objective neuropsychological examination was within the normal range, adjusted for age, gender, and years of education; (5) failure to meet the diagnostic criteria for MCI or AD dementia.
14.(Hong et al., 2014)	**Guidelines cited:** N/A. The presence of SCD was assessed by the question: “Do you feel that you have a declining memory?”.

15.(Koppara et al., 2015)	**Guidelines cited:** (Jessen et al., 2010; Peter et al., 2014; Scheef et al., 2012). The definition of SCD was based on the fact that participants were referred to the memory clinic for work-up of memory impairment and on a standard question: "Do you feel like your memory is getting worse?". To be classified as SCD in this study, the participants had to answer "yes, this worries me". Possible answers to this question were: "no"; "yes, but this does not worry me", and "yes, this worries me". This question has been validated with an increased hazard ratio for AD. SCD participants scored within ± 1.5 SD on any subtest of the Consortium to Establish a Registry of Alzheimer's disease (CERAD) battery. To rule out the presence of non-amnestic MCI participants in our SCD sample, CERAD Plus subtests trail making test A/B and S-Words were added to the assessment. They were considered SCD if they performed within the range of normal age, gender, and education adjusted normative cut-offs of –1.5 SD on these subtests.
16.(Lazarou et al., 2020)	**Guidelines cited:** (Molinuevo et al., 2017). Self-perceived memory decline compared to other cognitive functions, and in reference to others of the same age, occurring during the past five years as determined by the individual's medical history and psychological report, at an age cut-off of 60. Moreover, we additionally strived to exclude participants where other etiologies could explain self-perceived memory deficits, including vascular (examination of ischemic lesions of MRI, blood testing), psychiatric (interview, depression scale, psychoactive drugs, etc.) or other systematic etiologies, by carefully evaluating laboratory results, including blood samples, structural magnetic resonance imaging, the patient's medical history and additional questionnaires following the SCD-Initiative Working Group criteria.
17.(Lazarou et al., 2021)	**Guidelines cited:** (Dubois et al., 2014; Molinuevo et al., 2017).
18.(Lee et al., 2023)	**Guidelines cited:** (Jessen, Amariglio, et al., 2014). Self-experienced decline in cognitive capacity was evaluated among the subjects using the Memory Complaint Questionnaire (MAC-Q) (Youn et al., 2009) and the Subjective Cognitive Decline Questionnaire (SCD-Q) (Rami et al., 2014).

19.(Li et al., 2022)	**Guidelines cited:** (Abdulrab & Heun, 2008). (1) Self -reported cognitive decline (information was obtained through a standardised questionnaire, which asked: 1. Do you think you have memory loss? 2. If so, for years). 2 the onset age was more than 60 years old. (2) the presence of gradual memory decline had persisted for ≥6 months; (3) objective cognitive score in normal range.
20.(López-Higes et al., 2017)	**Guidelines cited:** (Jessen, Amariglio, et al., 2014). SCD participants came voluntarily to the Center for Cognitive Impairment Prevention (CCIP; Public Health Institute, Madrid City Council) to be evaluated due to their complaints about memory (in general). In accordance with the criteria set out in (Jessen, Amariglio, et al., 2014), these participants (1) presented mainly a subjective decline in memory; (2) their concerns (worries) about memory motivate medical consultation, that (3) are confirmed by a reliable informant; (4) seniors had the impression that subjective decline affects their daily activities; and (5) the onset of SCD was within the last 5 years.
21.(Luck et al., 2018)	**Guidelines cited:** N/A. Memory-related subjective cognitive symptoms (SCS) was evaluated with the following questions: (i) "Do you feel as if your memory is becoming worse?" (No/Yes); (ii) "If yes, does this worry you?" (No/Yes, this does worry me/Yes, this does worry me very much). Based on participants' response to question (i), participants were classified as having or not having memory-related SCS. Based on participants' response to question (ii), participants were classified as having either memory-related SCS without concerns, with some concerns, or with strong concerns (memory-related SCS subtypes).
22.(Macoir et al., 2019)	**Guidelines cited:** (Jessen, Amariglio, et al., 2014). (1) Self-experienced persistent decline in cognitive capacity in comparison with a previously normal status and unrelated to an acute event (SCD was assessed with the Questionnaire de De´pistage de la Plainte Cognitive ("Screening Questionnaire of Cognitive Complaint"; Dion et al. Unpublished data)) and (2) normal age-, gender-, and education-adjusted performance on standardised cognitive tests. The participants with SCD were all worried about their memory.

23. (Markova et al., 2019)	**Guidelines cited:** (Jessen, Amariglio, et al., 2014). Self-experienced persistent decline in cognitive capacity within the last 5 years in comparison with a previously normal status and unrelated to an acute event and normal age-, gender-, and education-adjusted performance on standardised cognitive tests.
24. (Morrison et al., 2023)	**Guidelines cited:** (Risacher et al., 2015). This healthy control group was subdivided into those with and without subjective cognitive decline using cognitive change index (CCI) scores (Rattanabannakit et al., 2016). Participants were considered SCD if they self-reported significant memory concern, quantified by a score of ≥16 on the first 12 items (representing memory changes) on the CCI.
25. (Moulinet et al., 2022)	**Guidelines cited:** N/A. SCD patients reported memory complaints and showed normal performance in all tests of the standardised neuropsychological assessment.
26. (Papadatos & Phillips, 2023)	**Guidelines cited:** (Chertkow et al., 2019; Jessen et al., 2020). Individuals were identified with SCD according to the following criteria: self-reported cognitive decline, though these individuals performed within the normal limits of the neuropsychological tests.
27. (Peng et al., 2023)	**Guidelines cited:** N/A. Subjective cognitive complaints were assessed by 12 questions using the Mandarin self-assessment questionnaire (Chao et al., 2022; Cheng et al., 2020, 2021). We grouped normal participants into "cognitively unimpaired (CU) with SCD-concern" and "CU with SCD-no concern" based on participants' responses to the additional question: "Generally, are you worry about that your daily life has been affected or even disturbed due to memory decline or the conditions mentioned above".

28.(Polcher et al., 2017)	**Guidelines cited:** (Jessen, Amariglio, et al., 2014). Normal cognitive performance and self-experienced cognitive decline with worries. The latter was operationalised with the following procedure: We assessed global and memory specific SCD, each by two consecutive questions. We first asked participants "Do you feel like your global cognitive performance has become worse?" (possible answers: yes/no). In case of a positive response to this initial question we further specified whether global SCD was experienced as worrisome by asking "Does this worry you?" (possible answers: yes/no). The same procedure was done for memory ("Do you feel like your memory has become worse?"). Self-experienced cognitive decline with worries was defined by endorsement of perceived decline with worries in global cognition and/or memory.
29.(Pusswald et al., 2016)	**Guidelines cited:** N/A. SCD classification required the presence of subjective memory deterioration as manifested by the seeking of medical help for memory problems and by the concurrent absence of any objectively, measurable cognitive deficits (mean z-score of each domain greater than −1.5 SD).
30.(Ren et al., 2023)	**Guidelines cited:** (Jessen, Amariglio, et al., 2014). 1. Subjective decline in memory; 2. occurrence within the last 5 years; 3. aged ≥50 years at the onset; 4. concerns associated with SCD; and 5. feeling of worse performance than peers. SCD without objective cognitive impairment were included in this study.
31.(Ribaldi et al., 2022)	**Guidelines cited:** N/A. The presence of subjective cognitive complaints (SCC) was investigated by the geriatrician through an ad hoc yes/no questionnaire: memory problems and their eventual impact on daily activities, language deficit, personality/behaviour change, disorientation in time and space, judgement/problem solving impairments, impact on daily living activities and on social participation. For the aim of the present study, the SCC total score was calculated as the sum of the self-reported impaired domains, with higher scores representing higher cognitive complaints (range: 0–10).
32.(Ruiz-Rizzo et al., 2022)	**Guidelines cited:** N/A. We defined SCD status by asking participants whether they perceived decline in their memory not related to particular health or personal events, and whether they were concerned about it. Only those who felt worrisome about the perceived decline in their memory were classified as having SCD.

33. (Sánchez-Benavides et al., 2018)	**Guidelines cited:** N/A. Participants were classified as SCD if the answer to the question "Do you perceive memory or cognitive difficulties?" was affirmative.
34. (Schmicker et al., 2023)	**Guidelines cited:** (Jessen, Amariglio, et al., 2014).
35. (Smart & Krawitz, 2015)	Although the Jessen (Jessen, Amariglio, et al., 2014) criteria for research classification of SCD were not available at the time of recruitment for this study, the recruitment of our resultant sample was broadly consistent with those guidelines; the SCD group had specific concerns about cognitive decline, whereas the Non-SCD group had no concerns. More specifically, first, we used self-report and neuropsychometric screening to rule out individuals with probable dementia or amnestic MCI. Second, we asked those remaining individuals to respond to the following question: "Are you concerned or worried that you are experiencing significant decline in your thinking abilities, more than just normal aging?".
36. (Snitz et al., 2015)	**Guidelines cited:** N/A. Presentation at a memory clinic where subjective concern regarding memory or thinking was a reason for seeking evaluation. normal neuropsychological test performance. Consensus adjudication of SCD.
37. (Sun et al., 2019)	**Guidelines cited:** (Jessen, Amariglio, et al., 2014). (1) self-experienced persistent decline in memory rather than other domains of cognition within the last 5 years, (2) concerns related to SCD and a feeling of worsened performance when compared to others of the same age group as expressed to physicians via the structured interview, (3) cognitive decline confirmed by an another informant, and (4) performance on standardised neuropsychological tests within age-, gender-, and education-adjusted norms and failure to meet the criteria for MCI or dementia.
38. (Tsai et al., 2021)	**Guidelines cited:** N/A. Participants who did not fulfil the criteria of MCI but reported current memory or cognitive difficulty were categorised into the SCD group.

39.(Vogel et al., 2022)	**Guidelines cited:** (Jessen, Amariglio, et al., 2014). They had SCD unrelated to an acute event; and 2) they had normal age-, gender-, and education-adjusted performances on standardised cognitive tests (one performance below expectation was accepted). The patients had all been referred to the memory clinic for a diagnostic evaluation and had therefore spontaneously expressed concerns of subjective impairment of memory as well as help-seeking behaviour. Since the SCD patients had worries associated with SCD, help-seeking behaviour, and specific memory complaints, they had at least three of the SCD-plus features listed in Jessen, et al. (2020).
40.(Wang et al., 2021)	**Guidelines cited:** (Jessen, Amariglio, et al., 2014; Mitchell et al., 2014). Self-experienced persistent decline in cognitive capacity relative to a previously normal cognitive status, unrelated to an acute event. All respondents were asked the following questions: 1) Do you have complaints about your memory? Participants were asked to answer "yes" or "no". 2) How long do you think your memory has declined? The participants were asked to respond with the duration of memory decline. 3) Are you worried about your memory problems? The participants were asked to answer "yes" or "no". If the answer was "yes", then the following questions were asked: 3.1 Are you worried about remembering something difficultly? 3.2 Are you worried about where things are placed? Are you worried about forgetting what you said? 3.4 Are you worried about forgetting a meeting or party? The participants were asked to answer with "mildly", "moderately", or "severely". Those who answered "yes" to the first question, who responded to the second question with a duration of memory decline of more than 0.5 years, and who indicated that the decline was unrelated to an acute event, satisfied the first criterion for SCD. The second criterion was normal performance on standardised cognitive tests used to classify MCI, adjusted for age, sex, and education.

41.(Yang et al., 2022)	**Guidelines cited:** (Jessen, Amariglio, et al., 2014). Self-reported persistent cognitive complaints of memory decline for 5 years or less; confirmation of cognitive decline by an informant; the age of 60 years or more at the onset of cognitive problems; feeling worse than peers of the same age and having concerns about SCD; performance within normal limits for age and educational attainment on cognitive screening measures, and Activities of Daily Living Assessment after adjustment for sex, age, and education; Global Deterioration Scale score of 2; Clinical Dementia Rating scale score of 0; and Hachinski Ischemic Scale score below 4.
42.(Yu et al., 2020)	**Guidelines cited:** (Abdulrab & Heun, 2008). (a) Belief that their memory has deteriorated in comparison to earlier life stages or to others of similar age; (b) diagnosis of adult onset of memory deterioration; (c) complaint of memory deterioration provided by the individual and/or confirmed by an informant. Normal scores on screening tests.
43.(Zheng et al., 2023)	**Guidelines cited:** N/A. Participants were divided into two groups according to their scores on the Chinese adaptation (Hao et al., 2019) of the nine-item Subjective Cognitive Decline Questionnaire (SCD-Q9) (Gifford et al., 2015). In the present study, the total SCD-Q9 score ranged from 0 to 7.5. According to the cutoff value recommended by (Hao et al., 2022) and the median SCD score (3 points) in this study, participants who scored equal to or below 3 were assigned to the Control group, whereas those who scored above 3 were assigned to the SCD group.
44.(Zhu et al., 2021)	**Guidelines cited:** N/A. (1) Self-perceived sustained memory decline within the last 5 years and confirmed; (2) not meeting the criteria for MCI and Clinical Dementia Rating score = 0.
45.(Zullo et al., 2021)	**Guidelines cited:** N/A. Participants underwent the “Questionnaire de la Plainte Cognitive” (QPC), a validated 10-item yes/no questionnaire assessing the presence of subjective cognitive difficulties in the last 6 months. According to the QPC scoring system, SCD is present when the subject answers “yes” to 3 or more items; and/or to item 5, and/or to items A, 4, 5, 7, 8.

Note: MCI = mild cognitive impairment, SCD = subjective cognitive decline.

Memory performance in SCD vs Non-SCD

The 45 studies provided data for 5,949 people with SCD and 8,470 people without SCD (Table 2.1). The overall weighted effect size for SCD participants versus Non-SCD participants was -0.24 (95% CI = -0.43, -0.04; $p = 0.019$; $I^2 = 95.83\%$; Figure 2.2), indicating that people with SCD performed significantly worse than people without SCD. The test for heterogeneity indicated significant variance across studies (Q = 1417.48, df = 44, $p < 0.001$), suggesting that the variance across effect sizes was greater than would be expected due to sampling error. Egger's regression test for funnel plot asymmetry was non-significant, indicating low risk of publication bias (z = 0.05, $p = 0.963$). A moderator analysis shows no moderating effect of recruitment source ($Q_M = 0.04$, df = 2, $p = 0.978$).

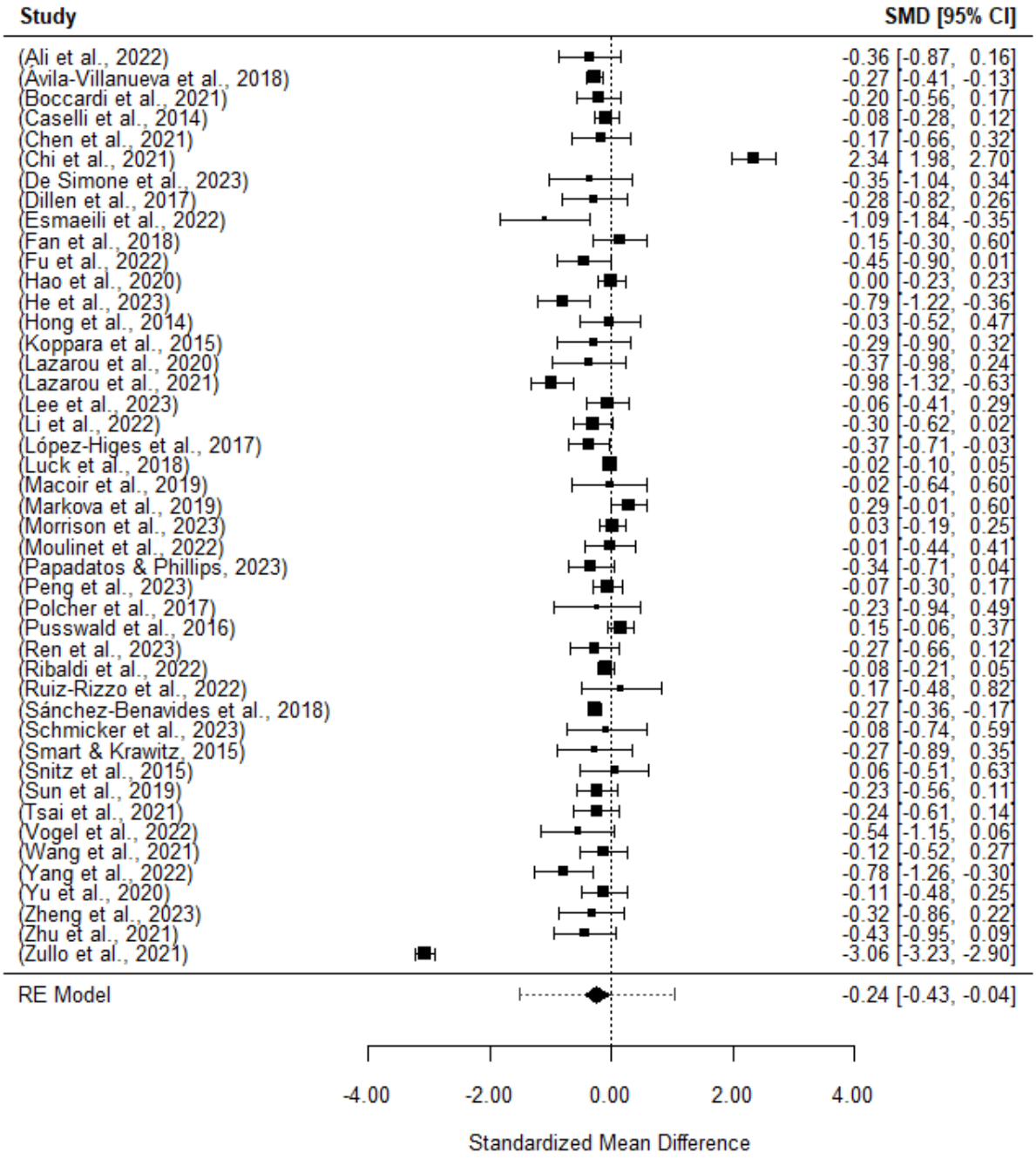

Fig. 2.2 *Forest plot of effect sizes and confidence intervals from each study contributing to the meta-analysis of SCD versus Non-SCD. Negative values indicate poorer performance by people with SCD versus people without SCD. SMD = Standardised mean difference*

Memory performance in SCD vs MCI

The 21 included studies provided data for 1,035 people with SCD and 2,119 people with MCI. The overall weighted effect size for SCD participants versus people with MCI was 1.53 (95% CI = 0.95, 2.11; $p < 0.001$; $I^2 = 97.47\%$; Figure 2.3), indicating that people with SCD

performed significantly better than people with MCI. The test for heterogeneity indicated significant variance across studies (Q = 320.88, df = 20, $p < 0.001$), suggesting that the variance across effect sizes was greater than would be expected due to sampling error. Egger's regression test for funnel plot asymmetry indicated a significant chance of publication bias (z = 3.00, $p = 0.003$). Duval and Tweedie's (2000) trim and fill was performed which suggested a minimal impact of publication bias on the results (Hedges' g = 1.53 (95% CI = 0.95, 2.11). A moderator analysis shows no moderating effect of recruitment source ($Q_M = 2.15$, df = 2, $p = 0.342$).

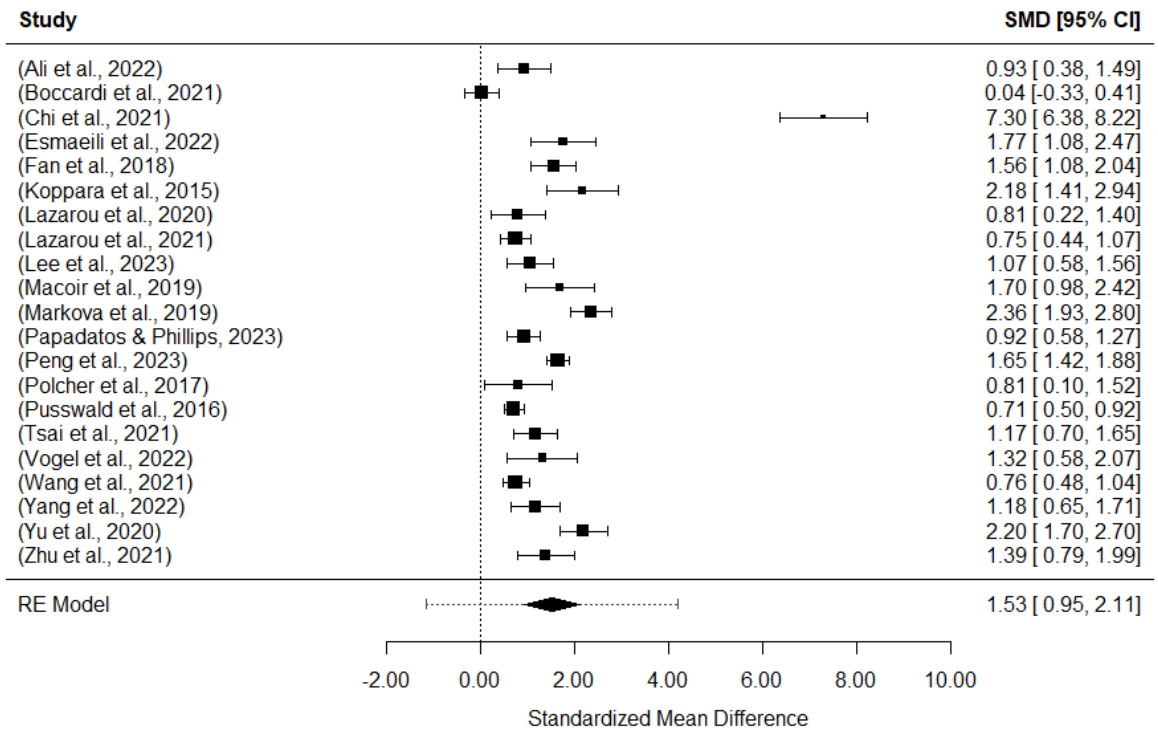

Fig. 2.3 *Forest plot of effect sizes and confidence intervals from each study contributing to the meta-analysis of SCD versus MCI. Positive values indicate better performance by people with SCD versus people with MCI. SMD = Standardised mean difference*

Study quality

Only two studies included in the review were assessed as having low risk of bias across all four QUADAS-2 domains (Table 2.3). The remainder were assessed to have high risk of bias or unclear risk of bias in at least one domain. Most studies did not report whether memory assessment was conducted blind to SCD status and therefore were rated as unclear risk of bias for the reference standard domain. Most studies where SCD participants were recruited via a memory clinic were assessed as 'high' risk of bias for the patient selection domain as the Non-SCD group were often recruited from a different source, whereas most studies where SCD was recruited from the community were rated as low on this domain as SCD and Non-SCD tended to be recruited from the same source and stratified into groups later. Given that one of our aims was to investigate the influence of recruitment source, it would be expected that studies recruiting SCD from memory clinics were unlikely to have recruited Non-SCD from the same source. However, recruitment source did not moderate the impact of group (SCD versus Non-SCD) on memory performance suggesting a minimal impact on our results. Most studies were rated as having low risk of bias in the index test domain. Those rated as high risk of bias for this domain tended not to have used (or cited) specific published criteria when defining SCD. In a small number of cases, this was due to lack of published criteria being available at the time (Caselli et al., 2014; Hong et al., 2014; Smart & Krawitz, 2015). Studies rated as high risk of bias for flow and timing tended to have reported memory performance in a subgroup of participants only or did not specify reasons for missing data.

Table 2.3 Study quality rating

Study	Risk of bias			
	Patient selection	**Index test**	**Reference standard**	**Flow and timing**
(Ali et al., 2022)	L	L	?	L
(Ávila-Villanueva et al., 2018)	L	L	L	L
(Boccardi et al., 2021)	?	L	?	L
(Caselli et al., 2014)	L	H	?	H
(Chen et al., 2021)	L	H	?	L
(Chi et al., 2021)	L	L	L	L
(De Simone et al., 2023)	H	L	?	L
(Dillen et al., 2017)	H	L	H	L
(Esmaeili et al., 2022)	?	L	?	L
(Fan et al., 2018)	H	L	H	L
(Fu et al., 2022)	H	L	?	H
(Hao et al., 2020)	?	L	H	H
(He et al., 2023)	L	L	?	L
(Hong et al., 2014)	?	H	?	L
(Koppara et al., 2015)	H	L	?	L
(Lazarou et al., 2020)	?	L	?	L
(Lazarou et al., 2021)	?	L	?	L
(Lee et al., 2023)	L	L	?	L
(Li et al., 2022)	L	L	H	L
(López-Higes et al., 2017)	L	L	?	L
(Luck et al., 2018)	?	H	H	L
(Macoir et al., 2019)	H	L	L	L
(Markova et al., 2019)	H	L	?	L
(Morrison et al., 2023)	H	L	H	H
(Moulinet et al., 2022)	H	H	?	L
(Papadatos & Phillips, 2023)	?	L	?	L
(Peng et al., 2023)	H	L	?	L
(Polcher et al., 2017)	H	L	H	H
(Pusswald et al., 2016)	H	H	?	L
(Ren et al., 2023)	L	L	?	L
(Ribaldi et al., 2022)	L	H	?	L
(Ruiz-Rizzo et al., 2022)	L	L	?	L

(Sánchez-Benavides et al., 2018)	H	L	?	L
(Schmicker et al., 2023)	H	L	?	H
(Smart & Krawitz, 2015)	H	H	?	L
(Snitz et al., 2015)	H	H	H	H
(Sun et al., 2019)	L	L	?	L
(Tsai et al., 2021)	L	H	?	L
(Vogel et al., 2022)	H	L	H	L
(Wang et al., 2021)	H	L	?	L
(Yang et al., 2022)	H	L	?	L
(Yu et al., 2020)	L	L	?	L
(Zheng et al., 2023)	L	L	?	L
(Zhu et al., 2021)	L	H	?	L
(Zullo et al., 2021)	H	L	?	L

Note: L = low risk of bias, H = high risk of bias, ? = unclear risk of bias.

Discussion

The present review found evidence for significantly reduced memory performance in people with SCD compared to people without SCD. Therefore, despite SCD being defined based on the absence of objective cognitive impairment, people with SCD show subtle impairment using detailed memory assessment. Screening tests are subjected to ceiling effects (Hoops et al., 2009). However, our results suggest that more detailed memory assessment is sensitive to subtle impairments in people with SCD. As would be expected, people with SCD performed significantly better than people with MCI (who would usually be classified as MCI based on objective memory impairment in line with clinical diagnostic criteria; Petersen et al., 2009). There was significant between-study heterogeneity in both outcomes, meaning that the pooled estimates must be interpreted as population average differences in accordance with the random effects meta-analysis model, whereas single studies may produce results which differ from the estimated average differences. The between-study heterogeneity may reflect methodological differences across studies, for example, in the criteria and methods used to

define SCD, with some defining due to individuals presenting to a memory clinic, while others used published criteria or a questionnaire. However, our results suggest that, on average, SCD is associated with subtle objective memory impairment which may indicate the earliest stages of dementia, at least for a subsample of people.

Across both meta-analyses, there was no moderating effect of recruitment source, meaning that SCD performed worse than Non-SCD and better than MCI regardless of whether they were recruited from a healthcare setting (suggesting help-seeking for concerns around SCD) or a community setting. This appears to contrast findings from Pike et al. (2022) who found that SCD participants recruited from a memory clinic were at higher risk of developing MCI than SCD participants recruited from a community setting. This observation might lead us to predict that people with SCD recruited from a memory clinic would be more likely to show subtle objective memory impairment in line with an increased risk of prodromal dementia. However, in the meta-analysis by Pike et al., (2022) people recruited from the community were still at elevated risk of conversion to MCI compared to people without SCD, suggesting that help-seeking alone cannot identify those with SCD who are at risk of conversion. Therefore, our results suggest that, despite their elevated risk of developing MCI compared to SCD recruited from the community, SCD participants recruited from a healthcare setting are no more likely to show subtle impairment on detailed memory assessment. This could reflect differences in baseline cognitive performance or education between people with SCD recruited from the community versus a healthcare setting. Indeed, a recent study (Zhao et al., 2021) found that, while people with SCD recruited from a memory clinic were more likely to show SCD plus criteria (which suggest increased risk of progression to dementia), they showed better neuropsychological test performance than people with SCD recruited from the community. Similarly, Kirsebom et al. (2017) found evidence for cognitive impairment in SCD which was not moderated by recruitment source

(memory clinic versus community). The present results are in keeping with these findings, and overall suggest that SCD appears to be associated with impairment in memory performance compared to Non-SCD regardless of recruitment source.

Limitations

There were methodological differences across studies included in the meta-analysis. In particular, there was considerable variation across studies in the methods used to define SCD, despite our aim to achieve greater consistency in this variable by limiting our search to studies published since 2014 (when the research criteria for SCD were published; Jessen, Amariglio, et al., 2014). Therefore, despite the publication of operationalised criteria for SCD, inconsistency remains across research studies in their definitions of SCD which may have affected the results of the present meta-analysis.

The publication of the additional 'SCD plus' criteria (Jessen et al., 2020) may provide further insights into potential moderators of memory impairment in SCD. A small number of studies (three) provided data for both a 'SCD' and a 'SCD plus' group but this was not enough data to conduct a meta-analysis of memory test performance across these two groups. More data comparing SCD and SCD plus would be valuable to investigate whether SCD plus is associated with greater risk of objective memory impairment. Given that, in the remainder of the papers included in the present meta-analysis the 'SCD' group would very likely include a mixture of people who do and do not meet the criteria for SCD plus, it is possible that differences in effects across the studies may be driven by people who would meet the SCD plus criteria.

Our methods for synthesising the literature comparing SCD and MCI on memory test performance were not especially precise since the primary aim of the review was to identify studies comparing SCD and Non-SCD. This means that a number of potentially eligible

studies of SCD versus MCI were not included if they did not feature a Non-SCD group. Indeed, our meta-analysis of the difference in memory performance between SCD and MCI indicated a significant chance of publication bias. Despite this, we view the results of this meta-analysis to be robust, given that individuals with MCI typically are categorised based on detectable memory impairment. Nevertheless, the overall estimate may not be especially accurate.

In the present meta-analysis, we combined effect sizes across episodic memory tests or subtasks where more than one was reported. We chose to do this to establish an estimate of overall memory performance. However, this method may obscure potential group differences across types of memory tasks e.g. verbal versus visual memory, or immediate versus delayed recall, and may have contributed to the significant between-study heterogeneity. Future research should seek to identify whether the type of episodic memory task is important in detecting subtle impairments in SCD. Further, this review focused on episodic memory performance since this is the cognitive domain thought to be most commonly affected in early Alzheimer's disease (Jessen, Wolfsgruber, et al., 2014) but subtle differences in other cognitive domains may also be evident in people with SCD (Macoir et al., 2019). Future research should expand on the present results to identify a "cognitive profile" of impairment which is characteristic of SCD and further explore whether the cognitive domains affected play a moderating role in risk of progressing to MCI.

Conclusions

The present meta-analysis adds to evidence that SCD can be a prodromal phase of MCI and dementia (Jessen, Amariglio, et al., 2014; Mitchell et al., 2014; Pike et al., 2022) given that SCD participants showed significantly impaired memory task performance compared to people without SCD. However, it is important to emphasise that most people who experience

SCD do not go on to develop dementia (Pike et al., 2022). Future research should aim to further explore potential moderators of the risk of objective memory impairment in people with SCD. Our results highlight the utility in detailed memory assessment for detecting subtle impairment in people with SCD which may provide clinical utility in exploring individual clinical risk of further decline.

Statements and declarations

Competing interests

The authors declare no conflicts of interest.

Data availability statement

The data that support the findings of the current research are available from the corresponding author on reasonable request.

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Appendices

APPENDIX 2A. PRISMA checklists

[NB: Appendix 2A is included in this section of the thesis portfolio as it is a required addition within the Journal submission.]

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract/Appendix
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Methods
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Methods
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for	Methods

Section and Topic	Item #	Checklist item	Location where item is reported
		obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Methods
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Methods
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Methods
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Methods
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Methods
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Methods
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Methods
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Methods
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Methods
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Methods
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Methods

Section and Topic	Item #	Checklist item	Location where item is reported
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Methods
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Methods
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	Results
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Results
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Results
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Results
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Results
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Results
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Results
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Results

Section and Topic	Item #	Checklist item	Location where item is reported
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion
	23b	Discuss any limitations of the evidence included in the review.	Discussion
	23c	Discuss any limitations of the review processes used.	Discussion
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Methods
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Methods
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Methods
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Title page
Competing interests	26	Declare any competing interests of review authors.	Statements and declarations
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Statements and declarations

Section and Topic	Item #	Checklist item	Reported (Yes/No)
ABSTRACT CHECKLIST TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			

Section and Topic	Item #	Checklist item	Location where item is reported
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	N/A
Registration	12	Provide the register name and registration number.	Yes

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

CHAPTER THREE: Empirical study

Reliability of online, remote neuropsychological assessment in people with and without subjective cognitive decline

Short title: Online neuropsychological assessment of subjective cognitive decline

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Abstract

Online, remote neuropsychological assessment paradigms may offer a cost-effective alternative to in-person assessment for people who experience subjective cognitive decline (SCD). However, it is vital to establish the psychometric properties of such paradigms. The present study (i) evaluates test-retest reliability of remote, online neuropsychological tests from the NeurOn software platform in people with and without SCD (Non-SCD) recruited from the general population; and (ii) investigates potential group differences in baseline performance and longitudinal change. Ninety-nine participants (SCD N = 44, Non-SCD N = 55) completed seven tests from the NeurOn battery, covering visual and verbal memory, working memory, attention and psychomotor speed. Thirty-five participants (SCD N = 17, Non-SCD N = 18) repeated the assessment six (+/- one) months later. SCD was classified using the Cognitive Change Index questionnaire. Test-retest reliability of the NeurOn test outcome measures ranged from poor to excellent, with the strongest evidence of reliability shown in the Sustained Attention to Response Test, Picture Recognition, and Trail-Making Test A. The SCD group was significantly older than the Non-SCD group so group differences were investigated using analysis of covariance whilst controlling for the effect of age. SCD scored significantly better than Non-SCD for Digit Span Backwards (maximum sequence length) and Picture Recognition (recall of object position). However, these were not significant when using the Bonferroni-adjusted alpha level. There were no differences between SCD and Non-SCD in longitudinal change scores. The results suggest online, remote neuropsychological assessment is a promising option for assessing and monitoring SCD.

Author summary

A considerable proportion of the older adult population experiences subjective decline in their thinking skills even though they score within 'normal' limits on screening tests for mild cognitive impairment or dementia. Research suggests that, for a small percentage of these people, their experience of a decline in their thinking skills might indicate an early stage of dementia. It is important for research to identify the earliest markers of dementia as this is when treatments may be most effective. By harnessing computing technology to improve on the accuracy and availability of cognitive assessments, we may be able to identify early and subtle cognitive changes caused by dementia. This study investigated whether online and remote cognitive assessment is a reliable method to assess and monitor thinking skills in the general older adult population. We were able to identify tasks which showed the best evidence for reliability when completed online and remotely by people with and without a subjective experience of cognitive decline, and therefore may be appropriate for monitoring thinking skills in people who are concerned about their cognitive ability. Our findings suggest online cognitive assessment may be a useful and cost-effective alternative to in-person clinic-based assessment.

Introduction

Cognitive and functional impairment associated with dementia places a significant burden on healthcare. This is projected to rise in line with the ageing population in the United Kingdom [1]. Research into treatments has been hampered by the lack of biomarkers for early or pre-symptomatic detection of neurodegenerative disease [2]. Pathophysiological changes of neurodegenerative disease occur years before symptom onset [3–5]. Therefore, earlier detection of dementia is a key priority for research as this is when disease-modifying treatments may be more effective [6,7]. There is emerging evidence that subtle cognitive changes are detectable years before diagnosis in sporadic neurodegenerative disease [6,8].

Neuropsychological assessment is a key tool for the detection and monitoring of cognitive impairment associated with dementia [9]. Better assessment methods are required to detect subtle cognitive changes in early disease stages [10]. The ability to harness advances in technology to collect more comprehensive and frequent data is a key area of interest in dementia research, including the use of digital methods for in-home monitoring of cognition [11]. Unsupervised, online neuropsychological assessment has the potential to increase the availability and frequency of cognitive assessments in order to detect and track subtle changes in cognitive ability [12].

It has been suggested that subjective cognitive decline (SCD) might be an early marker of cognitive impairment due to neurodegeneration [13]. SCD is the self-perception of a decline in cognitive performance despite unimpaired performance on standardised tests sensitive to mild cognitive impairment (MCI) or dementia [14]. Most people with SCD do not progress to MCI or dementia. However, research suggests they are at increased risk of doing so compared to people without SCD [14–16]. Specific factors have been identified to be associated with an increased risk of cognitive decline in people who experience SCD (known as the “SCD plus” criteria): subjective decline in memory, onset within the last five

years, onset at age 60+, persistence of SCD, presentation at a memory clinic, and informant-reported cognitive decline [14,15]. A recent meta-analysis identified additional risk factors for objective cognitive decline in people with SCD beyond the SCD plus criteria [17], including biomarkers of Alzheimer's disease pathology (e.g. high amyloid β/ high total tau protein in the brain and/or hippocampal atrophy), the presence of apolipoprotein E4 genotype, comorbid depression or anxiety, smoking status, fewer years of education, and poorer performance on a measure of executive functioning (investigated using Trail-Making Test B performance).

Given that most individuals with SCD will not progress to MCI, it is not recommended to monitor everyone. However, for those with additional risk factors, remote, online neuropsychology offers a low-cost method to assess and monitor cognition over time. Further, given the projected increase in the average age of people living in rural areas in England [1] remote assessment options offer a practical method to support accessibility of neuropsychological assessment services for rural populations [18]. Although such research is in its infancy, initial evidence suggests online neuropsychological assessment, completed remotely, can detect subtle deficits in cognition in people with SCD [19], therefore suggesting that this is a promising tool for the assessment and monitoring of SCD.

It is unclear whether online neuropsychological tests, completed remotely and unsupervised, show comparable psychometric properties to the 'gold-standard' in-person pen and paper tests. Various factors associated with online, remote test completion may impact on the reliability of results, such as technical issues, computer skills, cognitive and physical abilities affecting computer use, and a lack of supervision and additional instruction [20], meaning that equivalence to in-person tests cannot be assumed. A number of online neuropsychological assessment batteries have been developed which have shown low to high validity and reliability [21–26]. However, there is heterogeneity between the studies in terms

of study populations and methods used. Therefore, more data is needed in different populations particularly for online, remote neuropsychological assessment to inform its use in clinical practice [20,27]. The present study evaluates the reliability of remote, online neuropsychological tests, completed without supervision by people with and without SCD recruited online from the general population.

The primary objective of the study is to establish the test-retest reliability of online tests from the NeurOn software platform in people with and without SCD. A selection of NeurOn tests were previously found to have moderate test-retest reliability in healthy older adults and feasibility for completing remotely [25]. The secondary objective of the study is to characterise online neuropsychological test performance in people with and without SCD by investigating group differences in baseline performance and baseline-to-follow-up change. These objectives were achieved.

Hypotheses

We predicted that:

1. Online neuropsychological tests will show moderate test-retest reliability, in keeping with previous findings [25].
2. People with SCD will show subtle impairment in online, remote neuropsychological test performance compared to people without SCD (Non-SCD), in line with previous research [19].

Materials and methods

Ethical approval

Ethical approval was obtained from the University of East Anglia Faculty of Medicine and Health Sciences Research Ethics Subcommittee (ETH2223-0113). All participants provided informed consent electronically via an online consent form.

The Mantal and NeurOn software platforms

The Mantal software platform (https://mantal.co.uk/) from AAH Software Limited was developed by Alex Howard, Software Lead within the Norwich Research Park to facilitate the management of online clinical research studies. The NeurOn platform (https://neuropsychology.online/) was created by Professor Michael Hornberger in collaboration with Dr Emma Woodberry, Consultant Clinical Psychologist and Alex Howard, Software Lead as an alternative to in-person neuropsychological testing for clinicians and researchers. The NeurOn platform currently contains cognitive tests covering domains including memory, language, visuospatial ability, executive functioning and attention. Some standardised data are available and new tests are being developed. The tests feature randomised stimulus sets to allow longitudinal cognitive testing with minimal test-retest effects. NeurOn tests can be accessed within the Mantal software platform via an application programming interface. Therefore, participants are only required to create an account with one platform (Mantal) where they can then complete the relevant cognitive tests, pre-selected by the research team.

Test-retest reliability has been evaluated for a selection of the NeurOn tests (Reaction Time, a Go-No/Go test and the Virtual Supermarket Task) in a healthy control group who completed the online tests in-person (baseline) and remotely (follow-up), one week apart [25]. The four tests showed moderate test-retest reliability. In the present analysis, we

extended these findings by assessing test-retest reliability for a larger selection of NeurOn tests in SCD and Non-SCD groups, separately, and for fully remote participation.

Participants

Participants were included if they met the following eligibility criteria:

Inclusion criteria

- Age 60+ in line with the World Health Organisation definition of old age
- Capacity to give informed consent
- Sufficient computer literacy to complete the online Consent Form
- Fluent in English
- Access to a device (computer or laptop) for the completion of the study

Exclusion criteria

- A diagnosis of a neurological or neurodegenerative condition
- A diagnosis of mild cognitive impairment
- Being under the care of a secondary mental health service, due to the link between severe psychiatric disorders (and some pharmacological treatments) with cognitive dysfunction [28].

We aimed to recruit a sample size of 50 people per group (SCD; Non-SCD) based on similar studies of normative neuropsychological test data [29,30]. Longitudinal research studies with older adults have reported drop-out rates of between 5-37% [31,32]. Therefore, we aimed to recruit 120 participants to factor in an attrition rate in this region (assuming roughly 20%).

Recruitment

Recruitment began in April 2023. Participants were recruited via advertisement on social media, within the University of East Anglia campus, and via the National Institute for Health Research "Join Dementia Research" register (http://www.joindementiaresearch.nihr.ac.uk) in Norwich.

Procedure

The Participant Information Sheet was sent to potential participants via email along with a link to the study, hosted on the Mantal clinical research software platform. Potential participants were advised they could take as much time as they like to consider the information sheet. People who decided to take part in the study were able to register with the study website (using their email address) and complete an online consent form. After completing the consent form, participants were able to access an online eligibility screen which they were asked to complete by indicating whether they met each of the eligibility criteria via check boxes. If participants met all eligibility criteria they were then able to access the full baseline study session. Participants were instructed to use a laptop or desktop computer to complete the study as some of the current versions of the NeurOn tasks do not function correctly if the screen size is too small.

At the baseline session, participants provided demographic information before completing the study measures (mood questionnaires, SCD questionnaire, and NeurOn tests). The following demographic data were collected: age, sex, level of education (1 = did not complete GCSE, 2 = GCSE or equivalent, 3 = A Level or equivalent, 4 = Undergraduate degree or equivalent, 5 = Master's degree or equivalent, 6 = Doctoral degree), self-rated confidence using computers (1= not at all confident; 5 = very confident) since computer literacy may be related to online cognitive test performance [33], self-estimated average sleep

time, social interaction (measured using the Duke Social Support Index [34], Social Interaction subscale: max score = 12, with higher scores indicating greater social interaction), previous COVID-19 infection or long-covid since a previous infection has been shown to affect cognition [35], occupation, first part of postcode (as a proxy measure of socioeconomic status) and whether participants had a diagnosis of dyslexia. First part of postcode was converted to a socioeconomic status score using the Indices of Multiple Deprivation produced by the Ministry of Housing, Communities and Local Government [36] to derive an income deprivation percentage for the relevant local authority. Higher scores indicate greater levels of deprivation in the local authority area.

Participants were contacted by email five months after completing their baseline session to invite them to complete their six- (+/- one) month follow up session. Participants repeated the mood questionnaires and the NeurOn tests at follow up.

Measures

Participants completed the following measures online via the Mantal study website:

Assessment of subjective cognitive decline

Given the recruitment method precluded detailed screening of participants, we used a validated questionnaire to assess SCD, the 20-item Cognitive Change Index (CCI) [37]. The CCI was developed to assess cognitive complaints in older adults. We defined SCD as a score of 20 or above on the first 12 items of the CCI in accordance with recommendations by the developers of the measure [38]. Participants completed the CCI during the baseline session.

Mood questionnaires

Mood was assessed since there are well documented links between mood and cognitive performance [39]. The 15-item version of the Geriatric Depression Scale (GDS-15; [40]) was used to screen for depression. The maximum score is 15. A score of five or above indicates mild depression symptoms; a score of nine or above indicates moderate depression symptoms. The Geriatric Anxiety Inventory (GAI) [41] was used to screen for anxiety. The maximum score is 20. A score of nine or above indicates clinically significant anxiety symptoms. These scales were chosen as they were developed for use in older adult populations, therefore avoiding misattributing signs of normal ageing to depression or anxiety, and are well validated and commonly used.

Online neuropsychological assessment

Participants completed computerised neuropsychological tests from the NeurOn software platform within their Mantal account via an application programming interface within the Mantal study website. The tests can be completed using either touch screen or keyboard input, depending on the capabilities of the equipment used by participants. Participants completed the following tests in the order shown:

1. Picture Encoding: a stimulus encoding phase in which everyday objects are presented on screen at varying locations (top, bottom, left or right). Participants are instructed to remember the pictures and where on the screen they were presented.
2. Simple Reaction Time: participants are instructed to respond to repeated, on-screen stimuli as fast as they can.
3. Digit Span backwards (working memory): participants are required to remember a sequence of digits which are presented one by one on the screen. They must recall the

digits in reverse order. The length of the sequence increases until two trials of a sequence length are failed, ending the test.

4. Picture Recognition (visual memory): a recognition phase in which everyday objects (made up of a mixture of previously presented objects during the Picture Encoding phase, and novel objects) are presented on screen. For each item, participants must indicate whether they saw the object before. If they answer 'yes', they are then asked where on the screen the object was presented.
5. Word Encoding: a stimulus encoding phase in which a series of high-frequency words are presented on screen at varying locations (top, bottom, left or right). Participants are instructed to remember the words and where on the screen they were presented.
6. Sustained Attention to Response Test (attention): participants are presented with a series of digits and are instructed to respond to each digit apart from one (the 'no-go' target stimulus). There are 255 trials in the test, therefore requiring sustained attention over time. The task records reaction time, and will identify responses that are "too soon" or anticipatory (i.e. indicating responses that are faster than would be possible if following the rules of the task).
7. Word Recognition (verbal memory): a recognition phase in which a series of words (made up of a mixture of previously presented words during the Word Encoding phase, and novel words) are presented on screen. For each item, participants must indicate whether they saw the word before. If they answer 'yes', they are then asked where on the screen the word was presented.
8. Trail-Making Tests A and B (psychomotor speed, attention): participants are required to click 25 symbols in a certain order as fast as possible. For Trail-Making Test A participants must click numbered circles in order from smallest to largest, whereas for Trail-Making Test B they must alternate between numbers and letters in ascending order.

These tests were selected as they measure cognitive abilities commonly affected in early stages of dementia [42–44].

There was a delay of approximately 10 minutes between the picture/word encoding and recognition subtasks. The full neuropsychological test battery took approximately 20-30 minutes to complete. While the neuropsychological test battery was required to be completed in one sitting, participants were informed they could complete the neuropsychological tests and the questionnaires in separate sittings.

Analysis

The study used a longitudinal observational case-control design. Participants were grouped (SCD; Non-SCD) according to their score on the CCI. Test-retest reliability of the online neuropsychological tests was assessed in both groups, separately. Performance on the online neuropsychological tests at baseline and the change over time was compared between the two groups. The selected outcome measures for each cognitive test are detailed in Table 3.1.

Table 3.1 Outcome measures for each NeurOn test

NeurOn Test	Outcome measure	Direction of better performance
Digit Span Backwards	**N correct =** total number of correct sequences (max = 16)	↑
	N errors = total number of incorrect sequences	↓
	Max length = maximum sequence length correctly recalled (max = 9)	↑
Picture Recognition	**N correct** = total number of correctly recognised pictures and correct rejections of novel pictures (max = 30)	↑
	N position correct = total number of trials where the position of a recognised picture was correctly identified (max = 15)	↑
	False alarms = total number of 'false alarms', i.e. incorrect recognition of a novel picture	↓
Simple Reaction Time	**Average reaction speed** = mean reaction speed across correct trials (i.e. excluding incorrect trials)	↓
	N errors = total number of incorrect trials	↓
Sustained Attention to Response Test	**N correct** = total number of correct trials	↑
	Average reaction speed = mean reaction speed across correct trials (i.e. excluding incorrect trials)	↓
	N errors = total number of anticipatory and "too soon" responses	↓
Trail-Making Test A	**N errors** = total number of incorrect responses	↓
	Time to complete = total time taken to complete the task	↓
Trail-Making Test B	**N errors** = total number of incorrect responses	↓
	Time to complete = total time taken to complete the task	↓
Word Recognition	**N correct** = total number of correctly recognised words and correct rejections of novel words (max = 30)	↑
	N position correct = total number of trials where the position of a recognised word was correctly identified (max = 15)	↑
	False alarms = total number of 'false alarms', i.e. incorrect recognition of a novel word	↓

Where individual participants completed a baseline or follow-up session more than once, data from the first attempt of each task was always used. The exception was when it was clear they had encountered a technical issue on their first attempt and had therefore aborted the session and started again (evidenced either by no recorded responses to the task on their first attempt or the participant notifying the lead researcher of a problem).

At the time of writing, follow up data collection is ongoing. Data were last downloaded from the Mantal server on 8th February 2024 for the present analysis, at which time follow-up data were available for 35 participants.

Test-retest reliability was assessed using two-way mixed effects intraclass correlation coefficients (ICC) with absolute agreement as is recommended [45]. Koo and Li [46] suggest the following interpretation of ICC values: less than 0.5 indicates poor reliability, 0.5-0.75 indicates moderate reliability, 0.75-0.9 indicates good reliability, and greater than 0.9 indicates excellent reliability.

Chi-square test was conducted to investigate differences in sex, previous COVID-19 infection, long-covid prevalence, and dyslexia prevalence between the two groups. Continuous demographic data were assessed for normality using the Shapiro-Wilk test. The assumption of normality was violated for all continuous demographic measures. Therefore, Mann-Whitney U test was used to test for group differences (SCD versus Non-SCD) in these variables and group statistics reported using median and interquartile range. Analysis of covariance (ANCOVA) was used to explore group differences in baseline and baseline-to-follow-up change scores for each neuropsychological test outcome measure while controlling for the effect of age. Omega squared (ω^2) was used as a measure of effect size as it is less biased than other effect size measures in small samples [47]. Given each set of ANCOVAs examined 18 dependent variables (NeurOn test outcome measures), a Bonferroni-adjusted

alpha level of 0.05/18 = 0.003 was used for the ANCOVA results. Change scores were calculated by subtracting baseline scores from follow-up scores.

Data analysis was conducted using JASP (version 0.18.3) [48], R (version 4.0.2) and RStudio (version 2023.12.1) [49].

Results

Participant demographics

Figure 3.1 shows participation and completion rates for each part of the study. Twelve people registered and provided consent to participate but then did not complete the eligibility screen. Therefore, it is presumed they did not meet eligibility for the study. Two people did not complete the CCI and therefore were excluded from the group comparisons. 108 people (SCD N=47, Non-SCD N=61) completed the CCI and at least the study questionnaires. The demographics and questionnaire scores of the 108 participants are summarised in Table 3.2. All participants lived in the United Kingdom. The SCD group were significantly older than the Non-SCD group and scored significantly higher for depression and anxiety, however, the medians were well below the clinical range for both tests. As expected, CCI score was significantly higher in the SCD group.

Table 3.2 Participant demographics and questionnaire scores

	SCD	**N**	**Non-SCD**	**N**	**Test statistic**	***p***
Age, years	71.00 (12.00)	47	67.00 (8.25)	60	U = 1080.00	**0.038**
Sex (M/F)	20/27	47	20/41	61	X^2 = 1.09	0.297
Education level	4.00 (1.00)	46	4.00 (1.00)	61	U = 1687.50	0.061
Confidence using computers	4.00 (1.00)	47	4.00 (1.00)	61	U = 1553.00	0.424
Sleep (hours)	7.00 (2.00)	47	7.00 (2.00)	61	U = 1399.00	0.825
Social interaction	9.00 (3.00)	47	9.00 (3.00)	61	U = 1461.50	0.863
Prev. COVID-19 (Y/N)	26/21	47	42/19	61	X^2 = 2.09	0.149
N diagnosed with long-covid	1	47	1	61	X^2 = 0.04	0.852
Socioeconomic status score	10.60 (9.10)	47	8.10 (7.10)	61	U = 1321.00	0.481
N diagnosed with dyslexia	1	47	1	61	X^2 = 0.04	0.852
CCI	23.00 (6.50)	47	15.00 (4.00)	61	U = 0	< **0.001**
GDS-15	2.00 (3.00)	47	1.00 (2.00)	61	U = 846.00	< **0.001**
GAI	1.00 (4.50)	47	0.00 (2.00)	61	U = 1099.00	**0.028**

Note: data are presented as median (interquartile range) unless otherwise stated. CCI = Cognitive Change Index, GDS-15 = Geriatric Depression Scale-15 item version, GAI = Geriatric Anxiety Inventory.

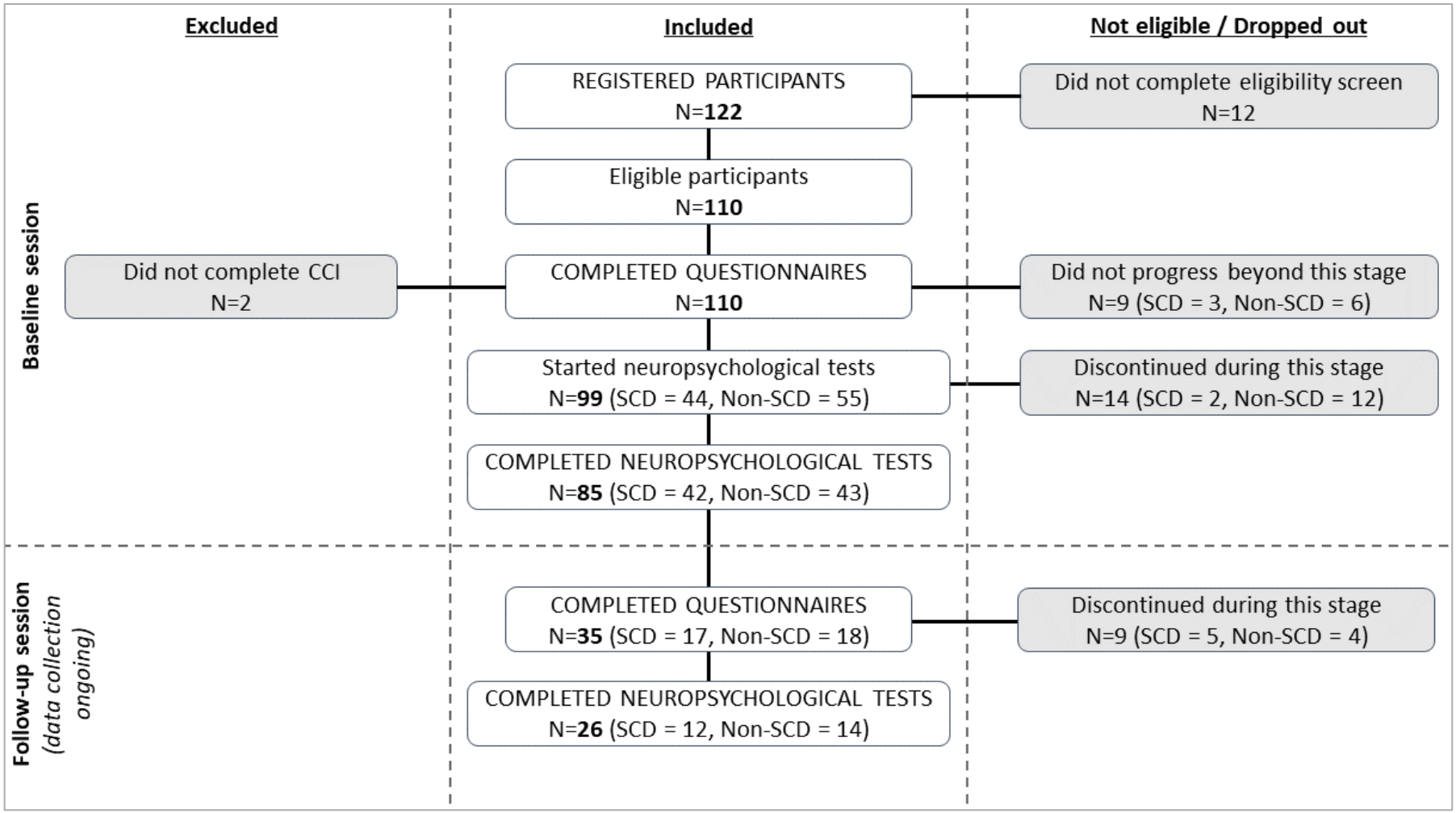

Fig 3.1 Participant flow diagram and study completion rates

Test-retest reliability

Table 3.3. shows the ICC values for each outcome measure, separated by group (SCD, Non-SCD). Two of the Digit Span Backwards outcome measures ('N correct', and 'Max length') showed moderate test-retest reliability in the SCD group. However, in the Non-SCD group, reliability was poor for all Digit Span Backwards measures. Word Recognition showed moderate to good reliability in the Non-SCD group, but poor reliability in the SCD group. Simple Reaction Time – 'N errors' showed moderate reliability in the SCD group but all other ICC values for this task indicated poor reliability. Trail-Making Test A – time to complete showed moderate reliability in both groups. Trail-Making Test B – time to complete showed moderate reliability in the SCD group only. ICC values for Picture Recognition indicated moderate to excellent reliability in the Non-SCD group for all measures, and moderate reliability in the SCD group for 'N position correct'. The Sustained Attention to Response Test showed moderate reliability in both groups, for all outcome measures.

Table 3.3 Test-retest reliability of NeurOn tests in each group

	SCD		Non-SCD	
Measure	**ICC**	**N**	**ICC**	**N**
Digit Span Backwards				
N correct	**0.68****	16	0.30	16
N errors	0.16	16	0.00	16
Max length	**0.59****	16	0.13	16
Picture Recognition				
N correct	0.40	15	**0.87*****	16
N position correct	**0.69****	15	**0.63****	16
False alarms	**0.43***	15	**0.97*****	16
Simple Reaction Time				
Average reaction speed	0.02	16	**0.44***	17
N errors	**0.56****	16	0.06	17
Sustained Attention to Response Test				
N correct	**0.56***	13	**0.58***	15
Average reaction speed	**0.68****	13	**0.64****	15
N errors	**0.68****	13	**0.67****	15
Trail-Making Test A				
N errors	0	11	0	14
Time to complete	**0.61***	11	**0.64****	14
Trail-Making Test B				
N errors	0	11	0.41	13
Time to complete	**0.57***	11	0.13	13
Word Recognition				
N correct	0.33	13	**0.82*****	15
N position correct	0.43	13	**0.64****	15
False alarms	0.21	13	**0.52***	15

Note: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. ICC = Intraclass correlation coefficient.

Group differences in online neuropsychological test performance

Eighty-five participants completed the full neuropsychological test battery (SCD N = 42, Non-SCD = 43; Figure 3.1). Up to 98 participants provided data for each individual test. The ANCOVA results for group differences in baseline neuropsychological test scores while controlling for age are presented in Table 3.4. The assumption of homogeneity of regression was tested for each ANCOVA and was non-significant for all. Using the unadjusted alpha level of 0.05, the SCD group scored significantly better than the Non-SCD group for Digit Span Backwards – 'Max length', and Picture Recognition – 'N position correct'. However, these were not significant when using the Bonferroni-adjusted alpha level of 0.003. There were no other significant group differences in baseline neuropsychological test performance.

Table 3.4 ANCOVA results for group differences in baseline neuropsychological test scores while controlling for the effect of age

	SCD		Non-SCD				
Measure	**M (SD)**	**N**	**M (SD)**	**N**	***F (df)***	***p***	ω^2
Digit Span Backwards							
N correct	6.46 (3.47)	44	5.70 (4.02)	54	2.72 (1, 95)	0.102	0.016
N errors	3.36 (1.30)	44	2.93 (1.23)	54	3.60 (1, 95)	0.061	0.026
Max length	4.93 (2.34)	44	4.24 (2.56)	54	4.17 (1, 95)	**0.044**	0.030
Picture Recognition							
N correct	28.21 (2.00)	43	27.20 (4.65)	54	2.01 (1, 94)	0.160	0.010
N position correct	12.44 (2.72)	43	10.98 (3.70)	54	4.60 (1, 94)	**0.035**	0.036
False alarms	0.54 (0.94)	43	1.11 (2.72)	54	1.80 (1, 94)	0.183	0.008
Simple Reaction Time							
Average reaction speed (ms)	376.70 (109.42)	44	354.13 (105.68)	54	0.51 (1, 95)	0.476	0.000
N errors	0.77 (3.33)	44	0.44 (1.14)	54	0.22 (1, 95)	0.643	0.000
Sustained Attention to Response Test							
N correct	107.54 (50.39)	43	105.44 (51.14)	48	0.08 (1, 88)	0.784	0.000
Average reaction speed (ms)	250.24 (122.37)	43	270.39 (140.21)	48	0.65 (1, 88)	0.422	0.000
N errors	103.84 (50.29)	43	104.35 (56.03)	48	0.29 (1, 88)	0.590	0.000
Trail-Making Test A							
N errors	0.88 (1.21)	42	1.61 (4.07)	44	1.40 (1, 83)	0.240	0.005
Time to complete (ms)	36647.15 (9280.90)	42	32576.49 (10164.89)	44	1.11 (1, 83)	0.295	0.001
Trail-Making Test B							
N errors	1.86 (2.95)	42	1.98 (3.58)	43	0.21 (1, 82)	0.645	0.000
Time to complete (ms)	54022.39 (20969.42)	42	47307.38 (54022.39)	43	0.15 (1, 82)	0.700	0.000
Word Recognition							
N correct	24.54 (2.87)	43	24.75 (3.42)	48	0.10 (1, 88)	0.757	0.000
N position correct	7.40 (3.15)	43	7.04 (3.91)	48	0.73 (1, 88)	0.396	0.000
False alarms	1.65 (1.79)	43	1.48 (1.75)	48	0.06 (1, 88)	0.810	0.000

Note: ms = milliseconds.

The ANCOVA results for group differences in baseline-to-follow-up change in scores while controlling for age are presented in Table 3.5. The assumption of homogeneity of regression was violated for the ANCOVAs of group differences in change scores for the Sustained Attention to Response Test – 'Reaction speed' and the Trail-Making Test B time to complete. There were no significant group differences in baseline-to-follow up change in neuropsychological test scores.

Table 3.5 ANCOVA results for group differences in baseline to follow up neuropsychological test change scores while controlling for the effect of age

	SCD		Non-SCD				
Measure	**M (SD)**	**N**	**M (SD)**	**N**	***F (df)***	***p***	ω^2
Digit Span Backwards							
N correct change	0.19 (2.90)	16	1.25 (5.69)	16	0.59 (1, 29)	0.447	0.000
N errors change	-0.19 (1.33)	16	0.88 (1.89)	16	3.89 (1, 29)	0.058	0.084
Max length change	0.13 (2.00)	16	1.06 (4.02)	16	0.90 (1, 29)	0.351	0.000
Picture Recognition							
N correct change	0.07 (3.22)	15	-0.38 (1.93)	16	0.14 (1, 28)	0.717	0.000
N position correct change	-0.13 (1.96)	15	-0.06 (2.35)	16	0.05 (1, 28)	0.823	0.000
False alarms change	0.33 (2.47)	15	0.19 (0.98)	16	0.08 (1, 28)	0.785	0.000
Simple Reaction Time							
Average reaction speed change (ms)	-6.46 (124.17)	16	42.78 (86.98)	17	2.25 (1, 30)	0.144	0.037
N errors change	0.25 (0.68)	16	2.47 (10.71)	17	0.85 (1, 30)	0.364	0.000
Sustained Attention to Response Test							
N correct change	-9.00 (49.98)	13	-4.87 (40.17)	15	0.16 (1, 25)	0.695	0.000
Reaction speed change (ms)	-16.13 (154.75)	13	-49.52 (91.74)	15	0.66 (1, 25)	0.425	0.000
N errors change	-0.08 (44.55)	13	4.67 (41.39)	15	0.00 (1, 25)	0.972	0.000
Trail-Making Test A							
N errors change	-0.08 (2.91)	12	0.29 (2.40)	14	0.44 (1, 23)	0.512	0.000
Time to complete change (ms)	956.08 (12779.57)	12	-1229.843 (5444.44)	14	0.49 (1, 23)	0.492	0.000
Trail-Making Test B							
N errors change	-0.17 (2.41)	12	-0.50 (1.70)	14	0.24 (1, 23)	0.629	0.000
Time to complete change (ms)	-2894.53 (19045.94)	12	7818.51 (21223.75)	14	1.81 (1, 23)	0.191	0.031
Word Recognition							
N correct change	0.46 (4.24)	13	-0.07 (2.25)	15	0.09 (1, 25)	0.763	0.000
N position correct change	-0.15 (3.76)	13	-1.13 (3.54)	15	0.22 (1, 25)	0.641	0.000
False alarms change	-0.23 (1.69)	13	0.27 (1.53)	15	0.45 (1, 25)	0.507	0.000

Note: ms = milliseconds.

Discussion

The aim of the current study was to investigate the test-retest reliability of online, remote neuropsychological assessment in people with and without SCD. Seven online neuropsychological tests were investigated, covering cognitive domains of visual and verbal memory, working memory, attention and psychomotor speed. There was poor to excellent reliability across all outcome measures. We predicted that the tests would show moderate reliability in line with a previous study [25], however the present study used a larger battery with different tests, and featured a greater number of outcome measures. Therefore, our results showed greater variability in terms of estimates of reliability. Overall, the best evidence of reliability was found for the Sustained Attention to Response Test, Picture Recognition, and Trail-Making Test A, as these showed moderate to excellent reliability across both groups for at least one outcome measure. These tests can be recommended for remote and repeated assessment.

A second aim of the study was to explore whether there are group differences (SCD versus Non-SCD) in baseline and longitudinal change in online neuropsychological test scores. At baseline, the SCD group scored significantly better than the Non-SCD group for Digit Span Backwards – 'Max length' (a measure of working memory), and Picture Recognition – 'N position correct' (a measure of spatial memory), which is opposite to what we predicted based on previous research [19]. However, these were not significant when using the Bonferroni-adjusted alpha level which accounts for multiple testing. Therefore, it is possible that these represent false positive results. Given that most of the research into cognition in SCD has employed in-person assessment, it was unclear whether subtle impairment would be detected using online, remote assessment, for which reliability can be impacted by factors specific to this method [20]. It is important to identify reliable online tests as a first step to exploring group differences in performance, and, given the subtle

differences reported in the literature to date [19,50], large sample sizes may be required to detect changes when using online assessment methods.

Our results suggest that NeurOn online neuropsychological tests have moderate test-retest reliability in people with SCD and Non-SCD, in particular the Sustained Attention to Response Test, Picture Recognition and Trail-Making Test A. In-person equivalents of these tests have shown test-retest reliability estimates of 0.76 (one week follow-up [51]), 0.60 (one-month follow-up, visual memory [52]), and 0.75 [53], respectively, in healthy control populations. Therefore, the online versions of these tests show comparable reliability, although slightly weaker, in this population of healthy older adults when completed remotely. This suggests that online, remote, completion of these tests appears to be a reliable method for monitoring changes in cognition in this population. This will be validated in the larger sample once follow up sessions are complete.

Limitations

There are a number of limitations to the present study. Some participants discontinued the baseline neuropsychological testing session and, therefore, there were missing data for the tests. This may have been due to the fully online, remote methodology (i.e. due to lack of additional instruction). Group sizes differed across neuropsychological tests for this reason. However, since the aim of the present research is to understand the feasibility of this methodology for research and clinical practice, this is likely an inevitable consequence of this study design. Future research should investigate whether the rate of non-completion during online, remote assessment paradigms is above that seen in studies using in-person/ supervised assessment methods. Reasons for non-completion were unclear unless participants contacted the lead researcher directly. Therefore, it is not possible to draw firm conclusions about factors contributing to discontinuation of testing in the present study.

There was no option to ‘skip’ a neuropsychological test during the testing session, meaning that if people encountered technical issues they would be unable to complete the later tasks. This may have reduced the sample sizes for neuropsychological tests towards the end of the battery.

As data collection is ongoing, the analysis of group differences in change in scores over time is preliminary. At present, the available follow-up sample size may be underpowered to detect significant group differences. Additionally for this reason we cannot formally measure attrition yet.

Our definition of SCD was based on the recommended cut-off score on a validated questionnaire (the CCI). This is in line with other studies which have defined SCD using the CCI [38]. However, this method may not completely map on to the definition of SCD proposed by the SCD-Initiative working group [54]. There is considerable variability across studies in the methods used to define SCD making it difficult to compare findings [55]. Therefore, it is not clear whether the finding of no group difference in performance between SCD and Non-SCD in the present study reflects differences in the tests used in the current study to those used in a previous study which found subtle impairment in SCD [19], or whether this reflects differences in the criteria used to define SCD across studies. This should be explored further. There is a need to improve consistency across studies in the definition of SCD. This study was conducted fully online, precluding in-person screening of SCD. It will be particularly important to establish the most suitable method of classifying SCD for online studies.

Finally, while the results of the present study show moderate reliability for a subset of the included tests when completed online and remotely, these results are not generaliseable to other online neuropsychological test platforms which may differ in ways to the tests assessed in the current study.

Conclusion

We found moderate test-retest reliability for NeurOn tests of memory, attention and psychomotor speed in people with and without SCD. Despite some drop out, the majority of participants completed the full test battery. This suggests online, remote neuropsychological assessment is a promising option for assessing and monitoring SCD, offering a cheaper alternative to in-person assessment and potentially increasing accessibility for some people. While there are practical issues to be resolved in future research, online and remote neuropsychological assessment has the potential to improve efficiency and accuracy of neuropsychological assessment.

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CHAPTER FOUR: Extended discussion and critical evaluation

Summary of the thesis aims

The aim of the current thesis was to investigate the utility of online, remote neuropsychological assessment for the assessment and monitoring of subjective cognitive decline (SCD) in older adults. The thesis firstly synthesised existing neuropsychological research in SCD to identify whether episodic memory impairment is detected using detailed neuropsychological assessment, to begin to identify a "cognitive profile" of SCD. An empirical study was then conducted to investigate the reliability of online, remote neuropsychological assessment in people with and without SCD, and whether group differences are evident in terms of baseline or longitudinal performance. The findings from these studies are summarised and critically evaluated below. Finally, recommendations for future research and clinical practice are presented at the end of this chapter.

Main contributions of the research

A systematic review and meta-analysis (Chapter Two) identified significantly worse episodic memory test performance in SCD versus people without SCD (Non-SCD) using detailed memory assessment. Despite this, SCD participants performed significantly better than mild cognitive impairment (MCI) participants. These findings suggest that detailed assessment (at least of episodic memory) is sensitive to SCD and may provide clinical utility in identifying people at risk of progression to MCI or dementia.

An empirical study (Chapter Three) found moderate test-retest reliability in online neuropsychological tests from the NeurOn platform, completely remotely by people with and without SCD. There was strong evidence for reliability for the Sustained Attention to Response Test, Picture Recognition, and Trail-Making Test A. Therefore, these tests can be

recommended for remote and repeated assessment in SCD. There were no group differences (SCD versus Non-SCD) in baseline or baseline-to-follow-up change scores on the NeurOn tests.

Strengths of the research

Systematic review

The systematic review protocol was pre-registered on the International Prospective Register of Systematic Reviews (PROSPERO). This is important for reducing bias, and enhancing transparency and reproducibility of research (Page et al., 2018). Two researchers independently screened the titles and abstracts of all papers retrieved during the initial search of the literature, further reducing the potential for bias. The methodology used during screening aimed to maximise the chance of including studies which met the inclusion criteria (e.g. including studies in the full text screen if they used any type of neuropsychological test or implied, but did not explicitly identify, memory assessment within the abstract). The review focused on episodic memory performance to reduce the impact of heterogeneity due to type of memory task. Forty-five studies were included in the meta-analysis, providing data for 5,949 SCD participants and 8,470 Non-SCD participants, meaning there was high statistical power for the detection of significant effects.

Empirical study

The empirical study used a validated and well-used measure to characterise SCD (the Cognitive Change Index (CCI)) (Rattanabannakit et al., 2016; Risacher et al., 2017). Mood was assessed using questionnaires which were developed for use in older adult populations to minimise the risk of misattributing signs of normal ageing to depression or anxiety (Pachana et al., 2007; Sheikh & Yesavage, 1986). Neuropsychological tests from the NeurOn battery,

which has previously shown initial evidence of test-retest reliability and feasibility for completing remotely (Morrissey et al., 2023), were used in the study. Different recruitment methods were used (e.g. research register, social media, local advertisement), improving the ability to reach potentially eligible participants (Bartlett et al., 2019). The study collected information about a large number of factors which may impact online cognitive test performance in older adults (e.g. age, sex, education, confidence using computers, sleep duration, social interaction, COVID-19 infection, socioeconomic status and mood) (Crivelli et al., 2022; Ferrie et al., 2011; Livingston et al., 2020; Robbins et al., 1996; Van Patten, 2021).

Limitations of the research

Systematic review

The systematic review was restricted to published papers since 2014 with the aim of capturing studies which classified SCD according to the SCD-Initiative research criteria (Jessen et al., 2014). Despite this, there remained considerable heterogeneity across studies in the criteria used to classify SCD. Therefore, an alternative method may have been more appropriate to reduce variation across studies in this domain, for example, by restricting the inclusion criteria to studies which used the SCD-Initiative to classify SCD. Further, there was not enough to data to explore whether the presence of 'SCD plus' (factors associated with increased risk of cognitive decline in people with SCD; Jessen et al., 2020; Slot et al., 2019) drove the significant episodic memory impairment observed in the SCD group.

The method of synthesising the literature comparing SCD and MCI was not especially precise, since the primary aim of the review was to compare SCD and Non-SCD. Therefore, many potentially eligible studies comparing SCD and MCI in episodic memory performance were not included in the meta-analysis. Effect sizes across episodic memory tasks were

combined to provide an estimate of overall episodic memory performance. However, this method may have obscured more nuanced information about the influence of type of episodic memory task (e.g. visual versus verbal, immediate versus delayed recall) on potential group differences in performance. Finally, although the studies included in the review were conducted across many countries, ethnicity was not consistently reported. Therefore, robust information about the representativeness of the participants was not captured in the present study.

Empirical study

Given the methodology of the study (i.e. fully remote and online participation) it was not possible to ascertain the reasons for discontinuation of the study by participants. The fact that some participants discontinued their baseline and/ or follow-up session meant that there was missing data and differing group sizes across neuropsychological test group comparisons. As data collection is ongoing, the findings using longitudinal test data are preliminary, and attrition cannot be formally measured yet. The fully online nature of the study precluded detailed assessment of SCD. Therefore, a validated questionnaire was used (CCI). However, this method of classifying SCD may not completely map onto the SCD-Initiative research criteria for SCD (Jessen et al., 2014). It is unclear whether the lack of group differences in performance in the present study reflect differences in the method used to define SCD, or whether it reflects differences between online, remote versus in-person assessment methods in the ability to detect subtle cognitive impairment in SCD. While the study collected information about socioeconomic status of participants, ethnicity was not collected. Therefore, the findings may be limited in their generalisability.

Implications of the research and recommendations for future directions

The results of the systematic review provide support to the hypothesis that SCD can represent preclinical dementia. The findings also highlight the utility of detailed neuropsychological assessment for detecting subtle cognitive changes in SCD. However, given that SCD is a common experience, the use of the concept within clinical practice is contentious (Howard, 2020) and it is important to emphasise that most people who experience SCD do not go on to develop dementia (Pike et al., 2022). Therefore, in clinical practice, it is not recommended to monitor everyone with SCD, however, it may be appropriate for those with additional risk factors for dementia. Nevertheless, given the interest in identifying the earliest stages of dementia for clinical trials of potential treatments (Aisen et al., 2013), the results suggest that SCD may be useful as a theoretical construct for research into dementia prevention. Future research into additional factors which moderate the risk of progression to MCI/ dementia in SCD would be valuable to allow further stratification for clinical trials, for example, whether there is a specific "cognitive profile" which indicates risk of further decline in SCD, or whether 'SCD plus' is associated with increased risk of episodic memory impairment in SCD. Importantly, given the heterogeneity across studies to date in the methods for defining SCD, future research should seek to achieve consensus in this regard to improve comparability of findings across studies.

The results of the empirical study suggest that online, remote neuropsychological assessment is a promising tool for assessing and monitoring cognition in SCD. Three of the tests showed moderate test-retest reliability and can be recommended for remote and repeated assessment of SCD. Future research is needed to clarify whether this method is sensitive to subtle cognitive impairment in SCD given the limitations identified in the current study. Although the results found good evidence for reliability for specific tests from the NeurOn battery, there are many additional factors (e.g. computer literacy, distractions, format of

instructions) which can influence online neuropsychological test performance. While these can be controlled for more easily using in-person study designs, more research is needed to understand how these factors may be measured or controlled for in online studies.

An important potential benefit of the use of online, remote neuropsychological assessment paradigms is their ability to increase the accessibility of neuropsychological assessment and to increase representativeness of participants within neuropsychological research. People from minority ethnic groups have been shown to be under-represented among NHS neuropsychological services (Teager et al., 2023) and within dementia research (Shaw et al., 2022). Further, people who live in remote or under-served areas, or who have physical health conditions may be excluded from in-person services or research studies (Adjorlolo, 2015; Barton et al., 2011; Brearly et al., 2017; Wadsworth et al., 2018). Future research should aim to establish whether online, remote neuropsychological assessment paradigms improve accessibility. However, it is also important to consider the need for some people to be able to access in-person assessment (i.e. for people who do not have access to or the ability to use the necessary technology for online neuropsychological assessment) (Hewitt et al., 2022; Sperling et al., 2023). In the present study, a number of participants discontinued their neuropsychological assessment session. While the reasons are unclear, it could suggest these individuals struggled to access the full study using the online, remote format. These issues will require careful consideration in future research and if implementing online, remote neuropsychology services. An integrated approach, with online paradigms supplementing traditional in-person assessment, may be the most appropriate way to ensure maximum accessibility (Sperling et al., 2023).

Conclusion

The studies contained in the present thesis provide evidence for subtle episodic memory impairment in SCD, and initial evidence to support the use of online, remote neuropsychological assessment of SCD. Further research is needed to identify factors which are associated with increased risk of subtle cognitive impairment and further cognitive decline in SCD. Online, remote neuropsychological assessment may offer a cost-effective alternative to traditional, in-person assessment methods. Careful consideration of issues of accessibility will be required when exploring the implementation of online, remote neuropsychological assessment clinically.

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Appendices

APPENDIX A

Neuropsychology Review Instructions for Authors
Taken from: https://link.springer.com/journal/11065/submission-guidelines?IFA

Manuscripts submitted to Neuropsychology Review should conform to the style of the American Psychological Association Publication Manual (6th edition: 2010). Neuropsychology Review is an EQUATOR adopter. The EQUATOR network represents a collaboration of researchers and journal editors who aspire to improve accuracy and transparency in research by promoting better reporting standards. Because Neuropsychology Review publishes review articles, the EQUATOR elements most relevant are the PRISMA guidelines for preparation and reporting of systematic reviews and meta-analyses (http://www.equator-network.org/reporting-guidelines/prisma/).
While narrative reviews will still be considered for publication when appropriate, Neuropsychology Review encourages publication of systematic reviews of treatment, intervention and diagnostic validity studies as well as systematic reviews of research relating to scientific questions in all aspects of clinical neuropsychology and behavioral neuroscience. Systematic reviews are enhanced by inclusion of a carefully conducted meta-analysis whenever appropriate. Authors of systematic reviews and meta-analyses submitted to Neuropsychology Review should prepare their manuscripts according to the PRISMA guidelines and include a PRISMA checklist (http://prisma-statement.org/PRISMAStatement/Checklist.aspx) with manuscript submission. When completing the checklist, authors should consider whether their manuscript requires editing to address all of the reporting requirements.
When undertaking systematic reviews, authors of submissions to Neuropsychology Review are requested not to use numerical rating scales that assign a single number to rank the quality of studies included in the review, for example, the Newcastle Ottowa Scale (NOS; for critique of the NOS see Stang, 2009, https://doi.org/10.1007/s10654-010-9491-z). Instead authors should separately rate or classify individual study quality and risk of bias criteria using established rating scales such as the QUADAS-2 checklist which can be adapted to review of any type of study and provides a graphic representation of the risk-of-bias of studies included in the review (Whiting et al., 2011 https://doi.org/10.7326/0003-4819-155-8-201110180-00009 see their Figure 3)
The QUADAS-2 criteria overlap with ratings included in the critical appraisal checklists (e.g., randomized controlled trials or diagnostic validity studies (http://www.cebm.net/critical-appraisal/)). For treatment and intervention studies key risk-of-bias criteria include, but may not be limited to, adequacy of randomization, pre-treatment equality of groups, blinding of patients, therapist or person undertaking outcome evaluation, adequacy of follow-up and objectivity in outcome measurement. For diagnostic validity studies, risk-of-bias criteria include representativeness of sampling, full information on the test-to-be-evaluated (the index test) and diagnostic group status (the reference standard) and independent, blinded acquisition of reference and index test information. Other risk of bias criteria may be important in some contexts including commercial or other conflict of interest.
Categorical risk of bias criteria can then be used in meta-regression of other examination of the influence of risk of bias on study results.
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In line with recent revisions to the use of I-squared (Borenstein et al. 2017 DOI: 10.1002/jrsm.1230), every time you report an analysis of heterogeneity, report the Q statistic, along with degrees of freedom and point estimate of significance, together with tau or tau-squared, and I-squared. De-

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Authors should avoid use of non-standard abbreviations. Avoid the use of a slash to join words in text. Re-write with a single word, or a hyphenated word, or a short phrase. In particular, 'and/or' can be re-written as 'or' which has the same logical meaning.
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Use italics for emphasis.
Use the automatic page numbering function to number the pages.
Do not use field functions.
Use tab stops or other commands for indents, not the space bar.
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Use the equation editor or MathType for equations.
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Abbreviations should be defined at first mention and used consistently thereafter.
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As noted above, avoid use of nonstandard abbreviations.

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Citation
Cite references in the text by name and year in parentheses. Some examples:
Negotiation research spans many disciplines (Thompson, 1990).
This result was later contradicted by Becker and Seligman (1996).
This effect has been widely studied (Abbott, 1991; Barakat et al., 1995; Kelso & Smith, 1998; Medvec et al., 1999).
Authors are encouraged to follow official APA version 7 guidelines on the number of authors included in reference list entries (i.e., include all authors up to 20; for larger groups, give the first 19 names followed by an ellipsis and the final author's name). However, if authors shorten the author group by using et al., this will be retained.
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Article by DOI Hong, I., Knox, S., Pryor, L., Mroz, T. M., Graham, J., Shields, M. F., & Reistetter, T. A. (2020). Is referral to home health rehabilitation following inpatient rehabilitation facility associated with 90-day hospital readmission for adult patients with stroke? *American Journal of Physical Medicine & Rehabilitation*. Advance online publication. https://doi.org/10.1097/PHM.0000000000001435
Book Sapolsky, R. M. (2017). *Behave: The biology of humans at our best and worst*. Penguin Books.
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Online document Fagan, J. (2019, March 25). *Nursing clinical brain*. OER Commons. Retrieved January 7, 2020, from https://www.oercommons.org/authoring/53029-nursing-clinical-brain/view
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Do not include large numbers of citations in text, for example, references retrieved through searches, or subsets analyzed separately in meta-anlysis. Instead, put blocks of citations in one or more Tables and the Tables referenced at the appropriate place in text.
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All tables are to be numbered using Arabic numerals.
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For each table, please supply a table caption (title) explaining the components of the table.
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Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and included beneath the table body.
Tables—additional information
Do not use faint lines or lettering and check that all lines and lettering within the figures are legible at final size.

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Supply all figures electronically.
Indicate what graphics program was used to create the artwork.
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No punctuation is to be included after the number, nor is any punctuation to be placed at the end of the caption.
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Research articles and non-research articles (e.g. Opinion, Review, and Commentary articles) must cite appropriate and relevant literature in support of the claims made. Excessive and inappropriate self-citation or coordinated efforts among several authors to collectively self-cite is strongly discouraged.
Competing Interests
Authors are requested to disclose interests that are directly or indirectly related to the work submitted for publication. Interests within the last 3 years of beginning the work (conducting the research and preparing the work for submission) should be reported. Interests outside the 3-year time frame must be disclosed if they could reasonably be perceived as influencing the submitted work. Disclosure of interests provides a complete and transparent process and helps readers form their own judgments of potential bias. This is not meant to imply that a financial relationship with an organization that sponsored the research or compensation received for consultancy work is inappropriate.

APPENDIX B

Modified version of QUADAS-2 for assessing study quality

Domain	**Signalling questions**
Patient selection	1. Are the demographics of controls and SCD well matched (and tested using t-test or equivalent)?
	2. Was the same recruitment source used for controls and SCD?
	3. Was the same screening process applied to controls and SCD?
Index test (SCD)	1. Does the definition of SCD capture the group of interest?
	2. Were published criteria identified in defining SCD?
	3. Was there sufficient screen of cognitive impairment at baseline?
Reference standard (memory assessment)	1. Were those assessing memory blind to SCD status?
	2. Was there no selectivity in reporting of test scores?
	3. Did all patients complete the memory tasks?
Patient flow and timing	1. Were all participants with memory data included in the analysis?
	2. Were reasons for missing data/dropout clear?

APPENDIX C

PLOS Digital Health Submission Guidelines

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When you first submit to the journal, providing you include all the necessary information needed for editorial assessment and review, we will not ask you to make any formatting changes. During resubmission, we may ask you to meet formatting requirements.

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Page and line numbers	Include page numbers and line numbers in the manuscript file. Use continuous line numbers (do not restart the numbering on each page).
Tables	Insert tables immediately after the first paragraph in which they are cited.
Supporting Information	Upload Supporting Information (SI) files separately.
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Language	Manuscripts must be submitted in English. You may submit translations of the manuscript or abstract as supporting information. Read the supporting information guidelines.
Abbreviations	Define abbreviations upon first appearance in the text. Do not use non-standard abbreviations unless they appear at least three times in the text. Keep abbreviations to a minimum.
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Equations	We recommend using MathType for display and inline equations, as it will provide the most reliable outcome. If this is not possible, Equation Editor or Microsoft's Insert→Equation function is acceptable. Avoid using MathType, Equation Editor, or the Insert→Equation function to insert single variables (e.g., "$a^2 + b^2 = c^2$"), Greek or other symbols (e.g., β, Δ, or ′ [prime]), or mathematical operators (e.g., x, ≥, or ±) in running text. Wherever possible, insert single symbols as normal text with the correct Unicode (hex) values. Do not use MathType, Equation Editor, or the Insert→Equation function for only a portion of an equation. Rather, ensure that the entire equation is included. Equations should not contain a mix of different equation tools. Avoid "hybrid" inline or display equations, in which part is text and part is MathType, or part is MathType and part is Equation Editor.

Nomenclature	Use correct and established nomenclature wherever possible.	
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	Drugs	Provide the Recommended International Non-Proprietary Name (rINN).
	Species names	Write in italics (e.g., *Homo sapiens*). Write out in full the genus and species, both in the title of the manuscript and at the first mention of an organism in a paper. After first mention, the first letter of the genus name followed by the full species name may be used (e.g., *H. sapiens*).
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Include a full title and a short title for the manuscript.

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Titles should be written in sentence case (only the first word of the text, proper nouns, and genus names are capitalized). Avoid specialist abbreviations if possible. For clinical trials, systematic reviews, or meta-analyses, the subtitle should include the study design.

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Authorship requirements

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Aim to highlight where your work fits within a broader context; present the significance or possible implications of your work simply and objectively; and avoid the use of acronyms and complex terminology wherever possible. The goal is to make your findings accessible to a wide audience that includes both scientists and non-scientists.
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Example Author Summary

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The introduction should put the focus of the manuscript into a broader context. As you compose the Introduction, think of readers who are not experts in this field. Include a brief review of the key literature. If there are relevant controversies or disagreements in the field, they should be mentioned so that a non-expert reader can delve into these issues further. The Introduction should conclude with a brief statement of the overall aim of the experiments and a comment about whether that aim was achieved.

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Submitted research should not rely upon retracted research. You should avoid citing retracted articles unless you need to discuss retracted work to provide historical context for your submitted research. If it is necessary to discuss retracted work, state the article’s retracted status in your article’s text and reference list.
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PLOS uses the reference style outlined by the International Committee of Medical Journal Editors (ICMJE), also referred to as the “Vancouver” style. Example formats are listed below. Additional examples are in the ICMJE sample references.

A reference management tool, EndNote, offers a current style file that can assist you with the formatting of your references. If you have problems with any reference management program, please contact the source company's technical support.
Journal name abbreviations should be those found in the National Center for Biotechnology Information (NCBI) databases.

Source	Format
Published articles	Hou WR, Hou YL, Wu GF, Song Y, Su XL, Sun B, et al. cDNA, genomic sequence cloning and overexpression of ribosomal protein gene L9 (rpL9) of the giant panda (Ailuropoda melanoleuca). Genet Mol Res. 2011;10: 1576-1588. Devaraju P, Gulati R, Antony PT, Mithun CB, Negi VS. Susceptibility to SLE in South Indian Tamils may be influenced by genetic selection pressure on TLR2 and TLR9 genes. Mol Immunol. 2014 Nov 22. pii: S0161-5890(14)00313-7. doi: 10.1016/j.molimm.2014.11.005. Note: A DOI number for the full-text article is acceptable as an alternative to or in addition to traditional volume and page numbers. When providing a DOI, adhere to the format in the example above with both the label and full DOI included at the end of the reference (doi: 10.1016/j.molimm.2014.11.005). Do not provide a shortened DOI or the URL.
Accepted, unpublished articles	Same as published articles, but substitute “Forthcoming” for page numbers or DOI.
Online articles	Huynen MMTE, Martens P, Hilderlink HBM. The health impacts of globalisation: a conceptual framework. Global Health. 2005;1: 14. Available from: http://www.globalizationandhealth.com/content/1/1/14
Books	Bates B. Bargaining for life: A social history of tuberculosis. 1st ed. Philadelphia: University of Pennsylvania Press; 1992.
Book chapters	Hansen B. New York City epidemics and history for the public. In: Harden VA, Risse GB, editors. AIDS and the historian. Bethesda: National Institutes of Health; 1991. pp. 21-28.
Deposited articles (preprints, e-prints, or arXiv)	Krick T, Shub DA, Verstraete N, Ferreiro DU, Alonso LG, Shub M, et al. Amino acid metabolism conflicts with protein diversity. arXiv:1403.3301v1 [Preprint]. 2014 [cited 2014 March 17]. Available from: https://128.84.21.199/abs/1403.3301v1 Kording KP, Mensh B. Ten simple rules for structuring papers. BioRxiv [Preprint]. 2016 bioRxiv 088278 [posted 2016 Nov 28; revised 2016 Dec 14; revised 2016 Dec 15; cited 2017 Feb 9]: [12 p.]. Available from: https://www.biorxiv.org/content/10.1101/088278v5 doi: 10.1101/088278
Published media (print or online newspapers and magazine articles)	Fountain H. For Already Vulnerable Penguins, Study Finds Climate Change Is Another Danger. The New York Times. 2014 Jan 29 [Cited 2014 March 17]. Available from: http://www.nytimes.com/2014/01/30/science/earth/climate-change-taking-toll-on-penguins-study-finds.html
New media (blogs, web sites, or other written works)	Allen L. Announcing PLOS Blogs. 2010 Sep 1 [cited 17 March 2014]. In: PLOS Blogs [Internet]. San Francisco: PLOS 2006 - . [about 2 screens]. Available from: http://blogs.plos.org/plos/2010/09/announcing-plos-blogs/.
Masters' theses or doctoral dissertations	Wells A. Exploring the development of the independent, electronic, scholarly journal. M.Sc. Thesis, The University of Sheffield. 1999. Available from: http://cumincad.scix.net/cgi-bin/works/Show?2e09
Databases and repositories (Figshare, arXiv)	Roberts SB. QPX Genome Browser Feature Tracks; 2013 [cited 2013 Oct 5]. Database: figshare [Internet]. Available from: http://figshare.com/articles/QPX_Genome_Browser_Feature_Tracks/701214

Source	Format
Multimedia (videos, movies, or TV shows)	Hitchcock A, producer and director. Rear Window [Film]; 1954. Los Angeles: MGM.

Supporting information

Authors can submit essential supporting files and multimedia files along with their manuscripts. All supporting information will be subject to peer review. All file types can be submitted, but files must be smaller than 20 MB in size.

Authors may use almost any description as the item name for a supporting information file as long as it contains an "S" and number. For example, "S1 Appendix" and "S2 Appendix," "S1 Table" and "S2 Table," and so forth.

Supporting information files are published exactly as provided, and are not copyedited.

Supporting information captions

List supporting information captions at the end of the manuscript file. Do not submit captions in a separate file.

The file number and name are required in a caption, and we highly recommend including a one-line title as well. You may also include a legend in your caption, but it is not required.

Example caption

S1 Text. Title is strongly recommended. Legend is optional.

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We recommend that you cite supporting information in the manuscript text, but this is not a requirement. If you cite supporting information in the text, citations do not need to be in numerical order.

Read the supporting information guidelines for more details about submitting supporting information and multimedia files.

Figures and Tables

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You can include figures in the main manuscript file at initial submission. If the manuscript reaches the revise stage, prepare and submit each figure as an individual file.

Cite figures in ascending numeric order at first appearance in the manuscript file.

For detailed instructions, read the guidelines for figures.

Figure Captions

If you are submitting a **new or revised manuscript**, place captions in a group at the end of the manuscript file.

After editorial acceptance, insert captions in read order in the manuscript text, immediately following the paragraph where the figure is first cited. Don't include captions as part of the figure files themselves or submit them in a separate document.

At a minimum, include the following in your figure captions:

A figure label with Arabic numerals, and "Figure" abbreviated to "Fig" (e.g. Fig 1, Fig 2, Fig 3, etc).

Match the label of your figure with the name of the file uploaded at submission (e.g. a figure citation of "Fig 1" must refer to a figure file named "Fig1.tif").

A concise, descriptive title

The caption may also include a legend as needed.

For detailed instructions, read the guidelines for figures.

Tables

Cite tables in ascending numeric order upon first appearance in the manuscript file.

Place each table in your manuscript file directly after the paragraph in which it is first cited (read order). Do not submit your tables in separate files.

Tables require a label (e.g., "Table 1") and brief descriptive title to be placed above the table. Place legends, footnotes, and other text below the table.

Read the guidelines for tables.

Data reporting

All data and related metadata underlying the findings reported in a submitted manuscript should be deposited in an appropriate public repository, unless already provided as part of the submitted article. Read our policy on data availability.
Repositories may be either subject-specific (where these exist) and accept specific types of structured data, or generalist repositories that accept multiple data types. We recommend that authors select repositories appropriate to their field. Repositories may be subject-specific (e.g., GenBank for sequences and PDB for structures), general, or institutional, as long as DOIs or accession numbers are provided and the data are at least as open as CC BY. Authors are encouraged to select repositories that meet accepted criteria as trustworthy digital repositories, such as criteria of the Centre for Research Libraries or Data Seal of Approval. Large, international databases are more likely to persist than small, local ones.
See our list of recommended repositories.
To support data sharing and author compliance of the PLOS data policy, we have integrated our submission process with a select set of data repositories. The list is neither representative nor exhaustive of the suitable repositories available to authors. Current repository integration partners include Dryad and FlowRepository. Please contact data@plos.org to make recommendations for further partnerships.
Instructions for PLOS submissions with data deposited in an integration partner repository:
Deposit data in the integrated repository of choice.
Once deposition is final and complete, the repository will provide you with a dataset DOI (provisional) and private URL for reviewers to gain access to the data.
Enter the given data DOI into the full Data Availability Statement, which is requested in the Additional Information section of the PLOS submission form. Then provide the URL passcode in the Attach Files section.
If you have any questions, please email us.

Financial Disclosure Statement
This information should describe sources of funding that have supported the work. If your manuscript is published, your statement will appear in the Funding section of the article.
Include your statement in the Financial Disclosure section of the initial submission form.
The statement should include:
Specific grant numbers
Initials of authors who received each award
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If they had no role in the research, include this sentence: "The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript."
If the study was unfunded, include this sentence as the Financial Disclosure statement: "The author(s) received no specific funding for this work."
Read our policy on disclosure of funding sources.
Competing interests
The corresponding author is asked at submission to declare, on behalf of all authors, whether there are any financial, personal, or professional interests that could be construed to have influenced the work. Any relevant competing interests of authors must be available to editors and reviewers during the review process and will be stated in published articles.
Read our policy on competing interests.
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When submitting a manuscript, all authors are asked to indicate that they do not have a related or duplicate manuscript under consideration (or accepted) for publication elsewhere. If related work has been or will be submitted elsewhere or is in press elsewhere, then a copy must be uploaded with the

article submitted to PLOS. Reviewers will be asked to comment on the overlap between related submissions.

Human subjects research

All research involving human participants must have been approved by the authors' Institutional Review Board (IRB) or by equivalent ethics committee(s), and must have been conducted according to the principles expressed in the Declaration of Helsinki. Authors should be able to submit, upon request, a statement from the IRB or ethics committee indicating approval of the research. We reserve the right to reject work that we believe has not been conducted to a high ethical standard, even when formal approval has been obtained.

Subjects must have been properly instructed and have indicated that they consent to participate by signing the appropriate informed consent paperwork. Authors may be asked to submit a blank, sample copy of a subject consent form. If consent was verbal instead of written, or if consent could not be obtained, the authors must explain the reason in the manuscript, and the use of verbal consent or the lack of consent must have been approved by the IRB or ethics committee.

All efforts should be made to protect patient privacy and anonymity. Identifying information, including photos, should not be included in the manuscript unless the information is crucial and the individual has provided written consent by completing the Consent Form for Publication in a PLOS Journal (PDF). Download additional translations of the form here. More information about patient privacy, anonymity, and informed consent can be found in the International Committee of Medical Journal Editors (ICMJE) Privacy and Confidentiality guidelines.

Manuscripts should conform to the following reporting guidelines:

Studies of diagnostic accuracy: STARD

Observational studies: STROBE

Microarray experiments: MIAME

Other types of health-related research: Consult the EQUATOR web site for appropriate reporting guidelines

Methods sections of papers on research using human subjects or samples must include ethics statements that specify:

The name of the approving institutional review board or equivalent committee(s). If approval was not obtained, the authors must provide a detailed statement explaining why it was not needed

Whether informed consent was written or oral. If informed consent was oral, it must be stated in the manuscript:

Why written consent could not be obtained

That the Institutional Review Board (IRB) approved use of oral consent

How oral consent was documented

For studies involving humans categorized by race/ethnicity, age, disease/disabilities, religion, sex/gender, sexual orientation, or other socially constructed groupings, authors should:

Explicitly describe their methods of categorizing human populations

Define categories in as much detail as the study protocol allows

Justify their choices of definitions and categories, including for example whether any rules of human categorization were required by their funding agency

Explain whether (and if so, how) they controlled for confounding variables such as socioeconomic status, nutrition, environmental exposures, or similar factors in their analysis

In addition, outmoded terms and potentially stigmatizing labels should be changed to more current, acceptable terminology. Examples: "Caucasian" should be changed to "white" or "of [Western] European descent" (as appropriate); "cancer victims" should be changed to "patients with cancer."

For papers that include identifying, or potentially identifying, information, authors must download the Consent Form for Publication in a PLOS Journal, which the individual, parent, or guardian must sign once they have read the paper and been informed about the terms of PLOS open-access license. The signed consent form should not be submitted with the manuscript, but authors should securely file it in the individual's case notes and the methods section of the manuscript should explicitly state that consent authorization for publication is on file, using wording like:

The individual in this manuscript has given written informed consent (as outlined in PLOS consent form) to publish these case details.

For more information about *PLOS Digital Health* policies regarding human subjects research, see the Publication Criteria and Editorial Policies.

Manuscripts describing observational clinical studies are subject to all policies regarding human research and community standards for reporting observational research as outlined by the STROBE statement. Furthermore, authors submitting work of this nature should pay special attention to the following requirements:

If the submitted manuscript is very similar to previous work, authors must provide a sound scientific rationale for the submitted work and clearly reference and discuss the existing literature.

The sampling strategy and eligibility criteria of enrolled subjects should be described in sufficient detail.

Sample size calculations should be justified with relevant inputs defined.

Independent and dependent variables considered for statistical analysis should be clearly defined and justified.

The validity and reliability testing of self-developed data collection tools should be reported.

Conclusions should be appropriate for the study design, with indications on how the study results will contribute to the base of academic knowledge.

APPENDIX D

University of East Anglia
Norwich Research Park
Norwich. NR4 7TJ

Email: ethicsapproval@uea.ac.uk
Web: www.uea.ac.uk

Study title: Characterisation of online, remote neuropsychological test performance in people with and without subjective cognitive decline

Application ID: ETH2223-0113

Dear Katie,

Your application was considered on 9th March 2023 by the FMH S-REC (Faculty of Medicine and Health Sciences Research Ethics Subcommittee).

The decision is: **approved**.

You are therefore able to start your project subject to any other necessary approvals being given.

If your study involves NHS staff and facilities, you will require Health Research Authority (HRA) governance approval before you can start this project (even though you did not require NHS-REC ethics approval). Please consult the HRA webpage about the application required, which is submitted through the IRAS system.

This approval will expire on **1st September 2024**.

Please note that your project is granted ethics approval only for the length of time identified above. Any extension to a project must obtain ethics approval by the FMH S-REC (Faculty of Medicine and Health Sciences Research Ethics Subcommittee) before continuing.

It is a requirement of this ethics approval that you should report any adverse events which occur during your project to the FMH S-REC (Faculty of Medicine and Health Sciences Research Ethics Subcommittee) as soon as possible. An adverse event is one which was not anticipated in the research design, and which could potentially cause risk or harm to the participants or the researcher, or which reveals potential risks in the treatment under evaluation. For research involving animals, it may be the unintended death of an animal after trapping or carrying out a procedure.

Any amendments to your submitted project in terms of design, sample, data collection, focus etc. should be notified to the FMH S-REC (Faculty of Medicine and Health Sciences Research Ethics Subcommittee) in advance to ensure ethical compliance. If the amendments are substantial a new application may be required.

Approval by the FMH S-REC (Faculty of Medicine and Health Sciences Research Ethics Subcommittee) should not be taken as evidence that your study is compliant with the UK General Data Protection Regulation (UK GDPR) and the Data Protection Act 2018. If you need guidance on how to make your study UK GDPR compliant, please contact the UEA Data Protection Officer (dataprotection@uea.ac.uk).

Please can you send your report once your project is completed to the FMH S-REC (fmh.ethics@uea.ac.uk).

I would like to wish you every success with your project.

On behalf of the FMH S-REC (Faculty of Medicine and Health Sciences Research Ethics Subcommittee)

Yours sincerely,

Dr Paul Linsley

APPENDIX E

Chief investigator
Dr Katie Peterson
Department of Clinical Psychology and Psychological Therapies,
School of Medicine,
University of East Anglia
Norwich
NR4 7TJ

PARTICIPANT INFORMATION SHEET

Characterisation of online, remote neuropsychological test performance in people with and without subjective cognitive decline

We would like to invite you to take part in our research study. Before you decide, it is important that you understand why the research is being done and what it would involve for you. Please take time to read this information, and discuss it with others if you wish. Please ask us if there is anything that is not clear, or if you would like more information.

What is the purpose of the study?

As people get older their risk for developing dementia increases. One of the key ways to assess for dementia is with pen and paper thinking tests which we call 'neuropsychological tests'. These are traditionally administered in hospital settings. However, since the COVID-19 pandemic there has been a greater need to be able to administer neuropsychological tests remotely (e.g., online). Currently, there is limited research about how useful these tests are when completed online. This study aims to explore this further by comparing online neuropsychological tests to traditional pen and paper tests.

Why have I been invited?

You have been approached because you have indicated that you would be willing to take part in an online study which involves completing neuropsychological tests, and you are a healthy volunteer. We are aiming to involve 120 people aged 60 and above who either have or have not experienced subjective cognitive decline over the last five years.

Do I have to take part?

No. Your participation in this research study is voluntary. If you agree to take part in the study you will be free to withdraw from the study at any time without explaining why.

What will happen to me if I decide to take part?

The study will involve taking part in an initial session and a follow-up session around six months later. If you agree to take part in the study, you will be provided with a link where you will be asked to complete a consent form and an eligibility screen to check whether you meet the eligibility criteria for the study.

If you provide consent to take part in the study and meet the eligibility criteria, you will be asked to complete some questionnaires about yourself (such as your age and years of education) and complete some neuropsychological tests online. These will include tests of thinking skills such as memory and attention. Importantly, the online neuropsychological tests are not validated for diagnostic clinical use, this means that your scores on the tests cannot be interpreted so you would not receive feedback about your performance. However,

the results will provide valuable information for validating the tests in future. The entire baseline session can be completed in one or two sittings of 30 minutes to 1 hour.

Six months later, we will get in contact to ask you to repeat the questionnaires and the neuropsychological tests for the follow-up session. Again, this session can be completed in one or two sittings of 30 minutes to 1 hour.

The online neuropsychological tests are contained within the Neuron software platform which is a company registered in the Norwich Research Park and was co-developed by Professor Michael Hornberger.

What should I consider?

In order to be eligible for this study your GP or healthcare professional should not have diagnosed you with any of the following: mild cognitive impairment; a neurodegenerative condition such as Alzheimer's disease; or a neurological condition such as stroke or traumatic brain injury. In addition, you would not be eligible to take part in the study if you are currently under the care of a secondary mental health service for a psychiatric condition.

You are free to participate in this study if you are also taking part in other research studies.

Are there any possible disadvantages or risks from taking part?

Some of the questionnaires will ask for health information. If you feel that some of the aspects discussed are related to you, we suggest for you to contact your GP to discuss this further.

What are the possible benefits of taking part?

There will be no direct benefits to you from participation in this study, but you will have contributed to research which may improve access to neuropsychological assessment services.

What if we find something unexpected and will my General Practitioner (GP) be informed of my participation?

Your GP will not routinely be informed of your participation in this research. The online neuropsychological tests are not validated for diagnostic clinical use so it is not possible to use the results to know if someone has performed worse than expected. Therefore, you would not be provided with results of the online neuropsychological tests, however if you are concerned about your memory or thinking skills we suggest for you to contact your GP to discuss further.

The study uses screening questionnaires for depression and anxiety which are validated. If you are happy for us to, we will notify your GP if your scores suggest moderate or severe levels of depression or anxiety.

Will my taking part in the study be kept confidential?

Yes. Any presentation or publication resulting from the research will use de-identified data and your identity will be kept strictly confidential.

We will keep all information about you secure. The University of East Anglia, as sponsor, is the data controller. This means that we, as University of East Anglia researchers, are responsible for looking after your information and using it properly. Data will be archived at the University of East Anglia for a minimum of 10 years after the study has finished.

Will I be reimbursed for taking part?

There will be an opportunity to enter a prize draw for a £25 Amazon voucher. You will be asked if you would like to opt in to the prize draw. If you say yes, your email address will be saved in a password-protected spreadsheet on a secure computer. This spreadsheet will be deleted after the prize draw has taken place.

What will happen if I don't want to carry on with the study?

Your participation in this research is voluntary and you may withdraw from the study at any time and request that your data be destroyed. If your de-identified data has already been published, or shared, then it cannot be withdrawn for those uses but will not be published or shared in the future.

What will happen to the results of this study?

The de-identified results might be presented at national and international meetings and published in medical or scientific journals.

De-identified samples may be sent to external collaborators and companies for further analyses. Relevant anonymous participant data will potentially be shared with UEA collaborators as well as national and international research collaborators that undertake other ethically approved research who all adhere to the latest data protection guidelines and confidentiality. Prior to sharing, all participant data will be made completely de-identifiable. Non-identifiable research data will remain accessible for a minimum of 10 years from publication. However, you can ask for your data to be destroyed at any time. If your de-identified data has been published, or shared, then it cannot be withdrawn for those uses but will not be published or shared in the future.

What if there is a problem?

If you are unhappy or have any concerns about how you have been approached or treated during the course of this study, please contact the lead researcher Dr Katie Peterson on k.peterson@uea.ac.uk in the first instance to try to resolve any issues. If still unsatisfied please contact the head of the department Professor Sian Coker on s.coker@uea.ac.uk.

Who has reviewed the study?

All research at the University of East Anglia is reviewed by an independent group of people, called a Research Ethics Committee, to protect participants' interests. This study has been reviewed and given a favourable opinion by the University of East Anglia Faculty of Medicine and Health Sciences Research Ethics Committee.

Participation in future research

If you agree to be contacted about future related research, your contact details (name and email address) would be held separately from this study on a password-protected spreadsheet on a password-protected computer in the University of East Anglia School of Medicine. Agreeing to be contacted does not mean you would be obliged to take part in future research.

Further information and contact details:

If you have any questions about the study or would like to speak to a member of the research team, please contact Dr Katie Peterson by email at k.peterson@uea.ac.uk.

Thank you for considering taking part in this study.

APPENDIX F

CONSENT FORM

Study title: Characterisation of online, remote neuropsychological test performance in people with and without subjective cognitive decline

Name of Researcher: Dr Katie Peterson

If you agree, please initial box

1. I confirm that I have read the information sheet dated……. (version ……..) for this study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason.	
3. I understand that data collected during the study may be looked at by individuals from the Sponsor (University of East Anglia) and from regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to access my data.	
4. I understand that the data obtained will be stored on secure networks within the University of East Anglia in accordance with current data protection guidelines (General Data Protection Regulation, GDPR, and the Data Protection Act 2018) and that only authorised members of the study team will have access to personally identifiable information.	
5. I agree to take part in this study.	
Optional:	
6. I agree to my GP being informed of my participation in this research if my scores on mood questionnaires suggest moderate or severe depression or anxiety, and for these scores to be shared with my GP. (Note: your GP will not be informed of your participation in this research unless you score within the moderate or severe range for anxiety or depression **and** you consent to this).	
7. I agree to be contacted about ethically approved research studies for which I may be suitable. I understand that agreeing to be contacted does not oblige me to participate in any further studies.	
8. I agree for my anonymised data to be used in future research which has ethical approval.	
9. I agree to my anonymised data being published and shared with University of East Anglia collaborators (which may include external collaborators and companies and national and international research collaborators) that undertake other ethically approved research and adhere to the latest data protection guidelines and confidentiality.	

Name	*Date*	*Signature*

APPENDIX G

Cognitive Change Index (CCI-20-S) (SELF REPORT VERSION)

Completed _____ in-person _____ phone

A. Do you feel like your memory is becoming worse? (Check only one)

☐ **No** ☐ **Yes, but this does not worry me** ☐ **Yes and this worries me**

B. Instructions:

This self-rating scale asks about your abilities, problem areas, daily functioning and activities. Please rate your **current** level of ability **compared to 5 years ago** and the severity of any current problems. Remember, you are describing how you are functioning now (meaning during the past month including today) compared to 5 years ago. Please rate any changes in your ability on the following 5-point scale, choosing the best fitting rating for each item describing a cognitive function or ability:

1. **Normal Ability (No Change or Better than 5 years ago)**: not a problem; no effect on daily activities; no assistance needed
2. **Slight/Occasional Problem (Minimal Change from 5 years ago)**: subtle; occurs less than once a week; may be slightly slower or less efficient; no assistance needed with ability; probably not noticeable to most other people
3. **Mild Problem (Some Change from 5 years ago)**: A bit worse, may perform related activity more slowly or less efficiently; occasionally may need a little help; may be noticeable to others
4. **Moderate Problem (Clearly Noticeable Change from 5 years ago)**: frequent problem; may affect complex activities on a daily basis or several times per week; often needs some assistance to perform complex activity
5. **Severe Problem (Much Worse than 5 years ago)**: continuous problem; unable to independently perform complex activity; requires ongoing assistance or supervision

Circle the number that best fits your current ability level compared to 5 years ago, using the scale from 1 to 5 below. Select the best choice for each item and *please do not skip any questions*:

Normal Ability	Slight/Occasional Problem	Mild Problem	Moderate Problem	Severe Problem
No Change *(compared to 5 years ago)*	Minimal Change *(compared to 5 years ago)*	Some Change *(compared to 5 years ago)*	Clearly Noticeable Change *(compared to 5 years ago)*	Much Worse *(compared to 5 years ago)*
1	2	3	4	5

1. Recalling information when I really try:	1	2	3	4	5
2. Remembering names and faces of new people I meet:	1	2	3	4	5
3. Remembering things that have happened recently:	1	2	3	4	5
4. Recalling conversations a few days later:	1	2	3	4	5
5. Remembering where things are usually kept:	1	2	3	4	5
6. Remembering new information told to me:	1	2	3	4	5
7. Remembering where I placed familiar objects:	1	2	3	4	5
8. Remembering what I intended to do:	1	2	3	4	5
9. Remembering names of family members and friends:	1	2	3	4	5
10. Remembering without notes and reminders:	1	2	3	4	5
11. People who know me would find that my memory is:	1	2	3	4	5
12. Remembering things compared to my age group:	1	2	3	4	5
13. Making decisions about everyday matters:	1	2	3	4	5
14. Reasoning through a complicated problem:	1	2	3	4	5
15. Focusing on goals and carrying out a plan:	1	2	3	4	5
16. Shifting easily from one activity to the next:	1	2	3	4	5
17. Organizing my daily activities:	1	2	3	4	5
18. Understanding conversations:	1	2	3	4	5
19. Expressing myself when speaking:	1	2	3	4	5
20. Following a story in a book, movie or TV:	1	2	3	4	5

APPENDIX H

Geriatric Depression Scale (short form)

Instructions: Circle the answer that best describes how you felt over the past week.

1.	Are you basically satisfied with your life?	yes	no
2.	Have you dropped many of your activities and interests?	yes	no
3.	Do you feel that your life is empty?	yes	no
4.	Do you often get bored?	yes	no
5.	Are you in good spirits most of the time?	yes	no
6.	Are you afraid that something bad is going to happen to you?	yes	no
7.	Do you feel happy most of the time?	yes	no
8.	Do you often feel helpless?	yes	no
9.	Do you prefer to stay at home, rather than going out and doing things?	yes	no
10.	Do you feel that you have more problems with memory than most?	yes	no
11.	Do you think it is wonderful to be alive now?	yes	no
12.	Do you feel worthless the way you are now?	yes	no
13.	Do you feel full of energy?	yes	no
14.	Do you feel that your situation is hopeless?	yes	no
15.	Do you think that most people are better off than you are?	yes	no

Total Score _____

APPENDIX I

Geriatric Anxiety Inventory

Please answer the items according to how you've felt in the last week.

**Tick the column under Agree if you mostly agree that the item describes you;
tick the column under Disagree if you mostly disagree that the item describes you.**

	Agree	Disagree
I worry a lot of the time.		
I find it difficult to make a decision.		
I often feel jumpy.		
I find it hard to relax.		
I often cannot enjoy things because of my worries.		
Little things bother me a lot.		
I often feel like I have butterflies in my stomach.		
I think of myself as a worrier.		
I can't help worrying about even trivial things.		
I often feel nervous.		
My own thoughts often make me anxious.		
I get an upset stomach due to my worrying.		
I think of myself as a nervous person.		
I always anticipate the worst will happen.		
I often feel shaky inside.		
I think that my worries interfere with my life.		
My worries often overwhelm me.		
I sometimes feel a great knot in my stomach.		
I miss out on things because I worry too much.		
I often feel upset.		

Original GAI reference: Pachana, N.A., Byrne, G.J., Siddle, H., Koloski, N., Harley. E., & Arnold, E. (2007). Development and validation of the Geriatric Anxiety Inventory. International Psychogeriatrics, 19, 103-114.