

Title page

Paper title: Psychosocial stress affects the acquisition of cerebellar-dependent sensorimotor adaptation

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- The specific role of the cerebellum in stress processing remains to be determined.
- We examined how stress modulated cerebellar-dependent saccadic adaptation.
- Psychosocial stress reduced the rate of saccadic adaptation.
- Greater cortisol output was associated with slower adaptation.
- These data demonstrate that stress modulates cerebellar-related functions.

Abstract

Despite being overlooked in theoretical models of stress-related disorders, differences in cerebellar structure and function are consistently reported in studies of individuals exposed to current and early-life stressors. However, the mediating processes through which stress impacts upon cerebellar function are currently unknown. The aim of the current experiment was to test the effects of experimentally-induced acute stress on cerebellar functioning, using a classic, forward saccadic adaptation paradigm in healthy, young men and women. Stress induction was achieved by employing the Montreal Imaging Stress Task (MIST), a task employing mental arithmetic and negative social feedback to generate significant physiological and endocrine stress responses. Saccadic adaptation was elicited using the double-step target paradigm. In the experiment, 48 participants matched for gender and age were exposed to either a stress (n=25) or a control (n=23) condition. Saliva for cortisol analysis was collected before, immediately after, and 10, and 30 minutes after the MIST. Saccadic adaptation was assessed 10 minutes after stress induction, when cortisol levels peaked. Participants in the stress group reported significantly more stress symptoms and exhibited greater total cortisol output compared to controls. The stress manipulation was associated with slower learning rates in the stress group, while control participants acquired adaptation faster. Learning rates were negatively associated with cortisol output and mood disturbance. Results suggest that experimentally-induced stress slowed acquisition of cerebellar-dependent saccadic adaptation, related to increases in cortisol output. These 'proof-of-principle' data demonstrate that stress modulates cerebellar-related functions.

Introduction

There is a critical need to understand the neural circuitry and associated neurocognitive mechanisms underlying stress-related psychiatric disorders in order to develop theoretically driven treatment and prevention strategies. While most researchers agree that stress, especially in early life has a significant effect on human development and the aetiology of many psychiatric conditions, the exact neurocognitive mechanisms remain unknown (Juster et al., 2011; McLaughlin et al., 2015; Norman et al., 2012). The available neurobiological models of stress-related disorders have predominantly focused on neural circuits connecting limbic-related regions e.g. amygdala, hippocampus, hypothalamus as well as the prefrontal cortex and the basal ganglia (Lupien et al., 2009; Peters et al., 2017). The cerebellum, is conspicuously absent from such neurocognitive models despite increasing evidence implicating this structure as a key region in aversive and arguably stressful emotion related processing (Adamaszek et al., 2017; Schutter, 2012).

Anatomical and functional studies in human and non-human species have demonstrated the existence of connections between the above-described stress-related regions and the cerebellum, particularly the vermis and midline cerebellum (Schmahmann and Pandya, 1997). Neurological cases with midline cerebellar lesions demonstrate psychiatric symptomatology, especially impaired stress reactivity (Schmahmann et al., 2007). Cerebellar structure and function is abnormal across multiple psychiatric diagnostic groups (Phillips et al., 2015) as well as in individuals suffering from acute or chronic effects of psychological trauma (De Bellis and Kuchibhatla, 2006; Walsh et al., 2014). Functional changes in the cerebellum have been reported following pharmacological treatment of depression and were associated with symptom improvements (Fu et al., 2004). Long-term neurostimulation treatment of the midline cerebellum

in schizophrenic individuals improved negative and depressive symptoms (Garg et al., 2016). Related to this, studies in healthy individuals subjecting participants to distressing, emotionally arousing states show cerebellar activations (Critchley et al., 2000; Damasio et al., 2000) and higher scores on emotion regulation related personality traits are associated with greater medial cerebellar grey matter volume (Tan et al., 2014). Studies in healthy individuals given cortisol, a key neurobiological marker of the stress response, show impaired memory and reduced activity in the cerebellum (De Quervain et al., 2003), and individuals with Cushing's disease demonstrate reduced cerebellar volume (Jiang et al., 2017). A contribution of the cerebellum in stress-related processing is therefore plausible, even more so given the presence of a high number of glucocorticoid receptors in this structure (Sanchez et al., 2000). Finally, worse behavioural performance on cerebellar-related tasks e.g. eye blink conditioning is evident under either acute stressful states (Duncko et al., 2007; Wolf et al., 2012; Wolf et al., 2009) and in individuals exposed to prior life-stress and deprivation (McPhillips and Jordan-Black, 2007; Roeber et al., 2014). While, some studies have shown that behaviour might be improved under stress (Duncko et al., 2007), this may be dependent on the nature of the stressor (psychosocial vs. physiological). Therefore, as a starting point for understanding the role of the cerebellum in the effects of stress, we investigated the effect of psychosocial stress on a cerebellar-dependent task, namely saccadic adaptation.

The cerebellum is a key structure in sensorimotor adaptation of saccadic eye movements (the quick, conjugate movements of the eyes to a new position between longer phases of fixation), a critical process that progressively restores optimal motor performance when repeated errors are consistently encountered (Pelisson et al., 2010; Prsa and Thier, 2011). Indeed, lesions to the cerebellum in human and non-human primates impair saccadic adaptation (Panouilleres et al., 2013; Takagi et al., 1998). Moreover, electrophysiological and lesions studies in non-human primates have demonstrated that the oculomotor vermis and the caudal part of the fastigial

nucleus are crucial for saccadic adaptation (Barash et al., 1999; Robinson et al., 2002). Finally, in humans, the involvement of these specific medio-posterior cerebellar areas in saccadic adaptation has been directly investigated using neuroimaging (Desmurget et al., 1998; Gerardin et al., 2012) and non-invasive brain stimulation (Jenkinson and Miall, 2010; Panouilleres et al., 2015). Given the key role of the medio-posterior cerebellum in both saccadic adaptation and stress-related processing, this process is an excellent candidate to explore the effect of acute stress on such cerebellar-dependent function. The aim of the present study was thus to determine the effect of acute stress on the cerebellum's ability in coordinating saccadic adaptation.

Saccadic adaptation was induced by generating an artificial inaccuracy using the classical double-step target paradigm (Mclaughlin, 1967). This paradigm consists in jumping the saccadic target to a new location at saccade onset. Because of saccadic suppression (Bridgeman et al., 2010; Matin, 1974; Zuber and Stark, 1966), participants are usually unaware of the target displacement. Saccadic eye movements are too fast to be corrected online and so, when the saccade ends, there is a mismatch between the eyes' goal and their final position. This is immediately corrected by a corrective saccade that acquires the goal of the initial action. When such mismatch is repeated over hundreds of trials, a progressive adaptation of saccade amplitude occurs, restoring the accuracy of the movements. The adaptive lengthening of saccades was achieved by jumping the target forward, i.e. along the saccade direction. Participants performed this saccadic adaptation after having received an acute stress condition or a control condition while the level of cortisol was assessed throughout the experiment. The adaptation abilities were compared between the control and the stress groups. We hypothesised that experimentally induced stress would reduce the degree of saccadic adaptation and that the degree of stress reported would be associated with the degree of saccadic adaptation.

Materials and Materials

Participants

Fifty-five participants were recruited in this study by advertisement in a participant database. Out of these, 7 participants were removed from the dataset due to artefact-contaminated eye-movement data (2), technical problems (2), protocol violations (2) and outliers in the cortisol data (1). Consequently, 48 healthy young adults were included in the analysis. Participants were randomly allocated to the stress (n=25) or control (n=23) groups (Table 1). Screening was conducted online. All were fluent English speakers, right handed, (verified with the Edinburgh Handedness Questionnaire (Oldfield, 1971)), aged 18 to 34 and had normal or corrected-to-normal vision. None had history of neurological trauma resulting in loss of consciousness, current or prior neurological or psychiatric illness. Exclusion criteria included current pregnancy, substance abuse, past or present use of psychotropic medication, as well as present consumption of steroid-based medication and any prescription medication taken for chronic illness or allergies. During the online screening, participants also reported their Body Mass Index (BMI). Two participants smoked less than 2 cigarettes/day.

A checklist was employed at the beginning of the experiment to document further participant information. Female participants reported use of hormonal contraception and date of last menstrual cycle. Females were either in the follicular (1-14 days post menses onset) or luteal phase (15 – 30 post menses onset) of their cycle. Secondary amenorrhea (no menstrual cycle) was established for one participant due to contraception. All participants reported having had a good night's sleep (7-8 hours). Within the hour before testing, none had engaged in any intense physical activity. Finally, none of the participants had consumed alcohol or smoked twelve hours

prior to the experiment. Sixteen participants reported caffeine consumption within the previous 12 hours (7 in the stress group).

Participants gave written consent and received monetary compensation for their participation.

The study was approved by the local ethics committee.

Trait measures

Eligible participants completed a series of online trait questionnaires. The following measures were presented in random order (Table 1): the Big Five Inventory (BFI-44) assessing extraversion, neuroticism, agreeableness, openness and conscientiousness (John et al., 2008); the Rosenberg Self-Esteem Scale (Rosenberg, 1965); the Schutte Self-Report Emotional Intelligence Scale (SSREIS), which determined four subscales, i.e., optimism, appraisal of emotions, utilisation of emotions and social skills (Schutte et al., 1998); the Parental Bonding Inventory (PBI), assessing maternal care and overprotection (Parker et al., 1979). These measures were chosen based on prior reports, indicating an association between such constructs and cortisol output. For example, increased diurnal cortisol secretion was demonstrated in individuals with high neuroticism (Garcia-Banda et al., 2014) and low self-esteem (Pruessner et al., 2004). In addition, emotional intelligence and maternal bonding may play a mediating role in the magnitude of the stress response (Engert et al., 2010; Mikolajczak et al., 2007). Therefore, these questionnaires were employed to ascertain that the two groups were balanced on measures with potential impact on endocrine output (Table 1).

State measures

Subjective measures of stress were collected before and after stress induction to assess mood. Participants completed the Profile of Mood States (POMS) questionnaire (McNair et al., 1971), which determined a total mood disturbance (TMD) score. According to author recommendations, the TMD score was computed by including the following subscales: tension, depression, anger, fatigue, confusion and vigour (McNair et al., 1971). Higher TMD scores indicated poorer mood. Visual analogue scales (VAS) were also employed with the following synonym pairs in random order: stressed-strained, calm-peaceful, tense-pressured, satisfied-content, threatened-vulnerable, nervous-anxious (Andrews et al., 2012).

Stress induction

The Montreal Imaging Stress Task (MIST) was employed to experimentally induce acute psychosocial stress (Dedovic et al., 2005). This is a validated paradigm shown to increase levels of cortisol and negative affect (Dedovic et al., 2009). The task consists of a series of mental arithmetic challenges with varying levels of difficulty, depending on condition (stress/control). Protocols in both conditions included a 1 minute practice and 2 subsequent task runs, each lasting 7 minutes. The stress condition enforced high failure rates by manipulating task complexity and strenuous time limits accompanied by a high pitched sound. Participants received negative feedback both from the program and the investigator. Particularly, a performance indicator compared participants' results with that of a fictitious user displaying high performing behaviour. Furthermore, in-between the runs, participants were told that results were unsatisfactory to reach minimum performance requirements. In the control condition, participants performed mental arithmetic of similar difficulty but without time constraints, sound or negative feedback by the program or investigator. Task delivery maintained a neutral tone. Participants were told to engage with the task in a relaxed manner.

Cortisol assessment

Cortisol levels were determined from saliva using salivettes (Sarstedt Inc., Quebec City, Canada). According to manufacturer information, saliva collection was done by participants by placing a swab in the mouth for 1-2 minutes. After collection, anonymized samples were centrifuged at 1000 g for 2 minutes. The resulting material was stored at -20°C until being shipped for biochemical analysis. Laboratory analyses were performed externally at the University Hospital of South Manchester. Cortisol was extracted by liquid chromatography with mass spectroscopy (LC-MS/MS). Inter- and intra-assay coefficients of variation were 8.4% at 5 nmol/L and 3.21% at 150 nmol/L.

Study protocol

The experimental sessions occurred in the afternoon 1:30pm – 6pm. Self-reported baseline mood (TMD + VAS) was assessed at the beginning of the session. Approximately 10 to 15 minutes after the start of the session participants provided the first saliva sample (baseline cortisol). This was followed by MIST-stress or MIST-control. Next, subjective mood was assessed again and participants provided the second saliva sample (cortisol t+1 min). A third sample was collected ten minutes after the end of the MIST (cortisol t+10 min). The saccadic adaptation task began approximately 12 minutes after the stressor/control at the expected peak cortisol time (Kuhlmann et al., 2005). Finally, soon after task completion, the fourth sample was collected to assess cortisol recovery to lower values following stress (cortisol t+30 min) (Figure 1). Trait measures were collected prior to the laboratory visit.

Eye-tracking setup and recordings

Participants sat 70 cm away from an 85 Hz computer screen (27° X 21°) on which the task was displayed on a grey background. The horizontal position of the right eye was recorded at 1000 Hz with the Eyelink 1000 eye tracker (desktop mount, SR Research, Canada). Each recording began with calibrating the eye tracker by fixating a 9 point sequence on the computer screen. The saccadic target was a black circle subtending 0.6° in visual angle.

Experimental design: saccadic adaptation task

A double-step target paradigm was employed to drive saccadic adaptation (Mclaughlin, 1967). There were 4 sequential blocks included in the task: preadaptation (24 trials), two adaptation blocks (2 x 70 trials) and postadaptation (24 trials).

In each adaptation block, there were 60 rightward adaptation trials and 10 leftward distractor trials. The two adaptation blocks were separated by a break (approximately 1 minute), during which participants were required to keep their eyes closed, in order to get a minute of rest and to not de-adapt. For the rightward adaptation trials, participants were instructed to fixate on the target presented in the centre of the screen for a random duration (700-1300ms).

Simultaneously with its disappearance, the target appeared 8° horizontally to the right of the centre. Once rightward saccades reached the rightward boundary of an invisible detection window (1.5° away from the centre), the target was displaced forward by 30% of the initial target eccentricity to induce an adaptive lengthening of rightward saccades (Figure 2). The final target was displayed for 500ms. The central fixation was illuminated again after a random duration (600–1200ms), signalling the beginning of a new trial. For the leftward distractor trials, targets were presented at 8° to the left of the centre and remained in this position for 500ms after saccade detection.

Preadaptation and postadaptation blocks were identical. Each included 12 rightward and 12 leftward trials. Trials began with participants fixating a central target presented for a random duration (700-1300ms). Simultaneously with fixation disappearance, the target was presented randomly 8° to the right or to the left of the screen centre. Participants were instructed to direct their gaze immediately as they detected the target. The target disappeared at saccade onset, allowing identification of baseline saccade metrics and aftereffects, respectively. A new trial began once the central fixation appeared again after a random duration (800-1300ms).

Data analysis

Saccadic adaptation data pre-processing

Horizontal saccades of the right eye were pre-processed offline using a custom-built Matlab script (MathWorks). Each primary saccade (trial) toward the target was automatically detected using the Eyelink parser (velocity threshold: 30°/sec) and manually inspected by the experimenter. The analysis considered all saccades that crossed the velocity threshold. Saccades contaminated by artefacts, such as blinks, saccades performed in the wrong direction and anticipated saccades were rejected (on average, $5.73 \pm 4.58\%$ of trials per session). Following pre-processing, saccade amplitude, duration, peak velocity and latency were calculated for all trials. Amplitude was computed as the difference between the final and initial position of the eye. Duration was calculated as the difference between the offset and onset times of the saccade. Peak velocity corresponded to the maximum velocity. Latency values were computed as the time between saccade onset and target appearance. Finally, gain values were based on the ratio of amplitude to retinal error. The retinal error was calculated as the difference between the initial position of the target and the saccade starting point, thus accounting for small variations in fixation. Changes in gain (rightward saccades) were computed

for each saccade in adaptation and postadaptation, relative to preadaptation (where n refers to the number of each saccade):

$$\text{Gain change saccade } n = \frac{\text{gain saccade } n - \text{mean gain preadaptation}}{\text{mean gain preadaptation}}$$

Finally, for each participant, rightward gain change trials were averaged in bins of 12 in the two adaptation blocks. This resulted in 10 bins, which showed adaptation over time. In preadaptation and postadaptation, relevant metrics were averaged for each participant, separately for each saccade direction. For each variable, leftward and rightward saccades with values outside +/- 2 SDs (mean of 12 trials in either the rightward direction in the pre-, adaptation and post trials, and mean of the 12 trials in the leftward direction in pre-adaptation) were excluded from further analysis. The two groups (control: $M=11.26$, $SD=6.38$; stress: $M=11.36$, $SD=6.11$) were matched in terms of the number of rightward adaptation saccades included in the analysis, following rejected trials and outlier exclusion ($t(46)=.05$, $p>.96$). Rightward saccades were submitted to statistical analysis, while leftward saccades were analysed in preadaptation only, to verify whether stress affected simple saccade metrics at baseline. Leftward distractor saccades in the adaptation blocks and leftward postadaptation trials were not analysed.

Statistical analyses

Statistical analyses were performed with the SPSS Statistics software package (IBM, Armonk, NY, USA). Saccadic adaptation, cortisol and mood data of the two groups were submitted to mixed model ANOVAs, with Greenhouse-Geisser correction. Where appropriate, simple group differences (e.g. at baseline, planned comparisons) were assessed using t tests (or non-

parametric equivalents). Nominal data was evaluated using the Pearson Chi-Square test or the Fisher's Exact Test where appropriate. The steepness of the adaptation slope was determined by calculating the slope of the linear fit on gain change over 120 rightward adaptation trials. The total cortisol output over time was computed by calculating the area under the curve with respect to the ground (AUC_g) (Pruessner et al., 2003). Given that many participants did show a decrease in cortisol over time, the analysis focused on AUC_g rather than AUC_i (Area under the curve with respect to increase from the first value), to have the index references to 0 (Pruessner et al., 2003). Pearson's correlations were also conducted to evaluate associations among stress indicators, adaptation parameters and trait measures (supplemental materials).

Results

Group characteristics at baseline

There were no differences between the stress and control groups on BMI ($t(46)=.87, p>.39$) and time of testing ($t(46)=-.98, p>.33$), as well as on cycle phase and use of hormonal contraception in the female sample (Fisher's Exact tests: $p>.10$). Groups did not differ significantly on gender ($\chi^2(1)=.01, p>.97$). The age of the stress group (range: 18-33, mean =23.04) and of the control group (range: 18-34, mean = 25.3) overlapped, despite a small tendency for the stress group to be slightly younger ($t(46) = -1.71, p>.09$). Baseline cortisol and baseline TMD scores were matched between groups ($t(46)=.63, p>.53$; $t(46)=.26, p>.80$). Group comparisons on baseline VAS scales also showed non-significant differences (Mann-Whitney U tests: $p>.22$). Finally, the two groups were matched in terms of trait measures (independent t tests: $p>.12$). Given that demographic, trait and baseline variables that might affect cortisol levels (e.g., testing times) were balanced between groups, differences in adaptation metrics are likely to arise from the stress manipulation.

Cortisol levels and mood

Stress-related cortisol and self-reported mood responses for the two groups are illustrated in Figure 3A and 3B, respectively. A mixed ANOVA on cortisol (Figure 3A) with Group factor (stress, control) and Time (baseline, t+1, t+10, t+30) revealed a main effect of time ($F(2,73)=9.58, p=.001$) and a main effect of group ($F(1,46)=4.79, p=.034$), but no significant interaction ($F(2,73)=2.32, p>.12$). Follow-up comparisons showed that cortisol levels were significantly higher in the stress group compared to the control group, 10 minutes ($t(38)=2.79,$

$p=.008$) and 30 minutes ($t(43)=2.79$, $p=.008$) after the MIST. Furthermore, AUCg was higher in the stress group compared to controls ($t(46)=2.15$, $p=.037$).

The MIST also induced group-specific changes in mood (Figure 3B). A mixed-design ANOVA with Group factor (stress, control) and Time (TMD pre-, post-MIST) yielded a significant interaction ($F(1,46)=23.85$, $p<.001$), a main effect of group ($F(1,46)=5.52$, $p=.023$), and no time effect ($F(1,46)=1.92$, $p>.17$). Mood changes evolved divergently for the stress and the control groups. Indeed, paired contrasts showed that baseline mood improved significantly after MIST-control (pre vs post: $p=.008$), while it significantly decreased after the stressor task (pre vs post: $p=.001$). Across groups, TMD post-MIST correlated positively with cortisol at $t+10$ ($r=.308$, $p=.033$) and with AUCg ($r=.342$, $p=.017$). For each group separately, these correlations were not significant ($p>.19$).

VAS synonym pairs assessing changes in mood, were submitted individually to Wilcoxon ranked tests, which revealed that participants in the stress group felt more stressed-strained ($Z=-3.67$, $p<.001$), tense-pressured ($Z=-3.87$, $p<.001$) and nervous-anxious ($Z=-2.73$, $p=.006$), as well as less calm-peaceful ($Z=-3.78$, $p<.001$) and satisfied-content ($Z=-3.90$, $p<.001$) after the MIST-stress task compared to baseline. All other comparisons, including within the control group, were not significant ($p>.05$).

In summary, the experimental manipulation determined greater cortisol output and increased negative affect following stress induction compared to control participants who exhibited lower cortisol levels and mood improvement over time.

Saccadic baseline performance

The 24 trials of the Preadaptation block allowed us to test whether the stress induction had a direct influence on saccade metrics. Separate mixed-design ANOVAs with Group factor (stress, control) and saccade direction (left, right) were conducted independently on saccadic gain, duration, velocity and latency. For both groups, rightward saccades had higher gains ($F(1,46)=23.62, p<.001$) and higher velocities ($F(1,46)=31.75, p<.001$) compared to leftward saccades. Saccade direction did not have an effect on duration and latency ($F(1,46)<.91, p>.35$). Results showed no main effects of group ($F(1,46)<.82, p>.37$) and no interactions with direction ($F(1,46)<.82, p>.37$) suggesting that stress exposure did not affect saccade parameters at baseline. We additionally checked group differences on trial-by-trial variability on rightward and leftward saccades separately, and found non-significant results (independent t tests: $p>.71$). This additional measure further emphasised that stress did not modulate baseline metrics.

Effects of stress on the adaptation time-course and after-effects

In the two forward adaptation blocks, displacing the target at saccade onset further away from the centre was employed to lengthen rightward saccade size. Saccade size increase over time was assessed by calculating gain change values relative to the preadaptation gain (Figure 4). By fitting a linear slope for each participant to the gain change values of 120 adaptation trials, we evaluated the rate of adaptation. Adaptation slopes were significantly steeper in the control group ($M=.08, SD=.06$) compared to the stress group ($M=.03, SD=.08$) ($p=.036$). We further investigated whether group differences in adaptation rates occurred at specific adaptation time points as learning progressed toward the end of the adaptation phase. Over 10 time points, a mixed ANOVA with Group factor (stress, control) and Time (10 bins) revealed a significant and progressive increase in saccade size over time in both groups ($F(4,181)=11.24, p<.001$). There was only a trend toward a significant time x group interaction ($F(4,181)=2.13, p=.08$), and the

group effect was not significant ($F(1,46)=.84, p>.36$). Over 2 time points (first and last adaptation bins), the same analysis showed an increase in saccade size over time ($F(1,46)=30.62, p<.001$), which interacted with group ($F(1,46)=4.43, p=.041$), suggesting that group differences became apparent toward the end of adaptation. Pairwise comparisons did not reach significance ($p>.13$).

Subsequently to adaptation, participants performed a postadaptation block, which revealed adaptation aftereffects. Change in gain postadaptation was computed relative to pre-gain. Gain change in the post block did not differ between the stress and the control groups ($p>.60$).

In summary, we found group specific changes in the rate at which adaptation was achieved at the end of adaptation compared to baseline gain change. Stressed participants adapted at a slower rate compared to controls. Despite this, adaptation aftereffects did not differ between groups.

Association between adaptation and stress measures

We evaluated whether adaptation was associated with measures of the stress response. Across both groups, changes in gain correlated negatively with AUCg toward the end of the adaptation block at bin 7 ($r=-.323, p=.025$) and marginally at bins 8 ($r=-.273, p=.060$) and 10 ($r=-.280, p=.054$). The slope of adaptation was negatively associated with AUCg: ($r=-.288, p=.047$) and TMD post-MIST: ($r=-.345, p=.016$). In summary, there was an overall increase in cortisol output and mood disturbance scores with decreasing adaptation at the level of the entire sample, particularly toward the end of the adaptation.

Saccade metrics associated with gain changes

Changes in duration and velocity were evaluated to establish their contribution to group-specific gain changes. Two-way mixed ANOVA with Group factor and Time reflecting changes over 10 bins, revealed a progressive increase in duration over time ($F(7,321)=8.68$, $p < .001$) and a significant interaction between time and group ($F(7,321)=2.33$, $p = .025$). Follow-up comparisons showed that saccade duration changes were larger in controls compared to the stress group at bins 7 ($p=.045$) and 10 ($p=.015$), matching the results of the gain changes. A two-way ANOVA with Group factor and Time (10 levels) performed on velocity changes yielded non-significant effects (all $F < 1.67$, $p > .14$). Duration and velocity postadaptation aftereffects did not differ between groups ($p > .10$). In summary, changes in duration, but not velocity metrics contributed to adaptation and these changes in duration, similarly to the gain, were affected by the stressor task.

Cortisol responders and non-responders

Individual differences in stress reactivity following MIST-stress have been reported (e.g. (Wolf et al., 2012; Wolf et al., 2009)). Despite the small sample size, a separate analysis was conducted to acknowledge these potential individual differences and provide further evidence in support of the association between AUCg and adaptation. Previous approaches defined responders and non-responders based on the upper and lower percentiles of the cortisol levels, thus eliminating bias associated with a median split (Kunz-Ebrecht et al., 2003). Consequently, for the current stress group, we characterized responders and non-responders as the top and bottom 30% AUCg cortisol values, respectively ($N=7$ in each group). Total cortisol output was significantly different between controls, responders and non-responders (one-way ANOVA: $F(2,34)=25.76$, $p < .001$), where top responders demonstrated significantly higher cortisol levels compared to non-responders ($t(12)=13.36$, $p < .001$) and controls ($t(26)=9.09$, $p < .001$).

For the saccadic adaptation data, results showed that adaptation slopes were different between the 3 groups (one-way ANOVA: $F(2,34)=4.61$, $p=.017$). Control participants showed steeper learning rates compared to top cortisol responders ($p<.001$). Other comparisons were not significant. Further, we evaluated group differences at specific adaptation time points. A two-way mixed ANOVA with Group factor (controls, responders, non-responders) and Time (10 bins) demonstrated an overall progressive increase in gain change in all groups ($F(4,151)=4.40$, $p<.001$). There was a significant interaction between time and group ($F(9,151)=2.0$, $p=.043$), followed by planned comparisons on bins 7-10 (end of the adaptation blocks). Gain changes were significantly smaller for top cortisol responders compared to controls at bins 7 ($p=.005$), 8 ($p=.032$) and 10 ($p=.020$), as well as compared to non-responders at bin 7 ($p=.032$) (Figure 5). Aftereffects did not differ between groups (one-way ANOVA: $F(2,34)=.83$, $p>.44$).

Finally, across groups, AUCg correlated negatively with gain change values at bin 7 ($r=-.407$, $p=.012$), bin 8 ($r=-.337$, $p=.041$), and bin 10 ($r=-.351$, $p=.033$), as well as with the adaptation slope ($r=-.404$, $p=.013$). Group-specific correlations were not significant ($p>.09$).

In summary, results suggest slower rates of learning in participants with the highest total cortisol output compared to non-responses and controls, particularly toward the end of adaptation. These results are consistent with the negative associations identified between AUCg and adaptation.

Discussion

This experiment assessed how acute experimentally induced psychosocial stress impacted upon saccadic adaptation, a putative task of cerebellar functioning. For participants in the stress group, the MIST stress manipulation was successful in maintaining a higher level of stress compared to controls, both subjectively, through mood changes, and physiologically, through greater cortisol output in the whole group. Although, both groups showed adaptation, stress modulated the rate at which adaptation was achieved. This effect became apparent toward the end of the adaptation and it was stronger in participants who demonstrated enhanced sensitivity to the stress manipulation, as indicated by the total cortisol output. Although saccadic adaptation has been used previously in different psychiatric populations (Coemans et al., 2014; Connolly et al., 2016; Mosconi et al., 2013), it is unclear in these studies whether performance differences are due to antecedents, concomitants or consequences of the disorder or medication effects. This study is the first to demonstrate that saccadic adaptation in healthy individuals is reduced following an experimental stress induction and that this adaptation level correlated with cortisol output.

In the present study, we find that control participants adapted quicker than stressed subjects, but exhibited similar aftereffects. There is robust evidence suggesting that behaviour during adaptation may be supported by two processes: one that adapts quickly from error but has only transient aftereffects, and one that demonstrates slow adaptation rates but has stronger retention (Smith, Ghazizadeh, & Shadmehr, 2006). Our present results could suggest that the fast process might have supported a quick adaptation in the control group, while this fast process may have been inhibited by stress, leading the stressed group to adapt at a slower pace. However, because the control group's adaptation mostly relied on the fast process, there

was more forgetting in this group. Conversely, the stressed group relied more on a slow process, and then the little amount of adaptation acquired was strongly retained. This would then explain the similar amount of adaptation retention in the two groups. Note that this explanation is tentative and that further studies with design such as the ones used in the studies by Xu-Wilson et al (2009) or Ethier et al, (2008) would be appropriate to test this hypothesis. Furthermore, it is interesting to note that patients with cerebellar lesions indeed lack the fast process of saccadic adaptation (Xu-Wilson et al., 2009) and mostly rely on the slow one, as we are proposing here for the stress group.

This is the first direct evidence that stress affects saccadic adaptation and therefore cerebellar functioning, potentially via an increase in glucocorticoid signalling. Although the neurobiological mechanisms underlying these effects remains to be clearly identified, we would like to speculate based on the previous literature. A recent meta-analysis investigating the neural correlates of psychosocial compared to physiological stressors (Kogler et al., 2015) appears relevant. Although both stressors induce endocrine responses and activated overlapping (inferior frontal gyrus and insula) brain structures, it appears that there are differences between these stressor types, in that psychosocial stress was specifically associated with a deactivation in the ventral striatum. Due to the anatomical connections between the basal ganglia and cerebellum (Bostan et al., 2013), such suppression of ventral striatum activity following psychosocial stress may inhibit cerebellar activity, and the computations involved in performing the saccade adaptation task (e.g. updating the internal model and learning from feedback). This interpretation is supported by recent work showing that the cerebellum computes expectations of reward (Wagner et al., 2017) and that reward processes can affect motor learning (Nikooyan and Ahmed, 2015) including saccadic adaptation (Kojima and Soetedjo, 2017; Meermeier et al., 2017). More research is needed to ascertain whether other forms of aversive or non-rewarding stimuli also reduce saccadic adaptation. Prior animal work has demonstrated that cortisol

administration reduces synaptic plasticity in the hippocampus (Maggio and Segal, 2012) and it would be important to establish how cortisol administration affects cerebellar-dependent saccadic adaptation.

The study acknowledges a number of limitations. There have been several reports of gender differences in terms of stress-induced susceptibility to learning (e.g. (Merz et al., 2013) but the current sample size lacked the power to detect such effects. Furthermore, the study included females taking hormonal contraceptives, who were either in the luteal or the follicular phases of their cycles, while it has been established that neuroendocrine responses to stress are modulated by sex hormones (Duchesne and Pruessner, 2013). Finally, approximately an hour of waiting should be allowed before collection of endocrine responses in order to yield an unbiased baseline value (Dickerson and Kemeny, 2004), which did not happen in the current study due to time constraints.

Considering these limitations, the study should be considered as demonstrating 'proof-of-principle' results on the potential modulating effects of psychosocial stress on cerebellar-dependent saccadic adaptation. However, it is important to generalise this research beyond the present study. Future research should evaluate whether stress might determine the same directional effect on learning in other sensory-motor domains, not necessarily associated with midline cerebellar regions, such as reaching, walking or balancing (Bastian, 2011). Finally, further studies are needed in clinical or vulnerable groups with prior stress exposure e.g. (Walsh et al., 2014) shown to have reduced cerebellar volume, in order to understand whether reduced saccadic adaptation is also present, despite no current stressor.

As reported above, prior reviews describing neurocognitive models of stress have focused on limbic-regions and impairment on more declarative forms of memory (Lupien et al., 2009; Peters

et al., 2017). This earlier work might imply stress negatively affects all aspects of task performance. Recent work has suggested that not all brain memory systems are negatively affected by stress, but rather have discussed a trade-off between hippocampal and striatal memory systems under stress conditions (Goldfarb and Phelps, 2017; Schwabe and Wolf, 2013). Nevertheless, it is still unknown how cerebellar-memory systems are affected by stress. In a general sense at the level of the organism, it is arguably adaptive for organisms to suspend learning when the world is stressful i.e. uncertain or ambiguous (Koolhaas et al., 2011; Schwabe et al., 2010) as learning is metabolically costly and resources need to be conserved (Peters et al., 2017). To relate this to the cerebellum, theoretical models of cerebellar functioning state that the cerebellum generates and updates internal sensory-motor predictive models of 'what usually happens' in order to aid preparation for action (Ito, 2008; Sokolov et al., 2017). Based on our data we propose that under stress, the updating of cerebellar-internal models is inhibited, either directly via glucocorticoid signalling, or indirectly via the basal ganglia (see above). Future work needs to examine further the consequences on brain function and behaviour of such an inhibition effect. If occurring at vulnerable points in development, this inhibition could impair the growth and maturation of cerebellar structures as previously reported (De Bellis and Kuchibhatla, 2006; Walsh et al., 2014). However, more research studies are necessary to develop this hypothesis.

In conclusion, we show that a prior psychosocial stressor modulates the cerebellar-dependent saccadic adaptation and the degree of stress experienced, as indexed by cortisol, which in turn is associated with the degree of saccadic adaptation. This work will advance evidence-based knowledge and the further elaboration of models needed to understand the neural circuitry and associated neurocognitive mechanisms underlying stress-related psychiatric disorders. Such knowledge can then be applied to develop theoretically driven and mechanistic, treatment and prevention strategies for stress-related disorders.

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Table and Figure captions

Table 1

Note. Unless otherwise specified, numbers depict group averages followed by SD in brackets.

▲ VAS data shows mean ranks. Acronyms represent: Body Mass Index (BMI), Total Mood Disturbance (TMD), Profile of Mood States (POMS), Visual Analogue Scales (VAS), Big Five Inventory (BFI - 44), Schutte Self-Report Emotional Intelligence Scale (SSREIS), Parental Bonding Inventory (PBI). Group differences do not reach statistical significance thresholds.

Δ Cycle phase could not be established for one participant due to reported amenorrhea.

Figure 1

Note. Baseline cortisol was collected approximately 10-15 minutes after participant arrival; subsequent collections occurred immediately after the stress manipulation, as well as 10 and 30 minutes later; assessment of mood was conducted before and after the MIST; the saccadic adaptation task took place 10 minutes after stress induction.

Figure 2

Note. Forward adaptation protocol; target was initially displayed at 8° following a random fixation period; the detection window limit triggered the target to be displaced at 10.4°; the wider black line shows a saccade toward the initial and displaced target.

Figure 3A and 3B

Note. 3A. Overall cortisol output is greater in the stress group, with significantly higher values 10 and 30 minutes after the MIST. ** $p < .01$. 3B. Negative mood was greater after the stress manipulation; conversely, control participants reported improved mood following MIST-control. ** $p < .01$.

Figure 4

Note. Gain change developed at a slower rate in the stress group; despite achieving larger gain changes, control participants demonstrate poor retention.

Figure 5

Note. Slow-paced learning rates were more pronounced in the top 30% cortisol responders; non-responders exhibited behaviour similar to that demonstrated by the control group. ** $p < .01$ (responder – control at bin 7), * $p < .05$

Table 1. Participant characteristics

	Stress	Control
N	25	23
Age	23.04 (4.56)	25.30 (4.57)
Gender (females)	14	13
BMI	23.08 (3.21)	22.33 (2.81)
Time of testing	2:55 pm (1:12)	3:16 pm (1:16)
Hormonal contraception (females)	7	2
Menstrual cycle (follicular: luteal)	8 : 5 ^A	9 : 4
TMD baseline (POMS)	26.56 (27.28)	24.74 (21.34)
Stressed – Strained baseline (VAS rank) [^]	25.20	23.74
Calm – Peaceful baseline (VAS rank)	25.58	23.33
Tense – Pressured baseline (VAS rank)	24.08	24.96
Satisfied – Content baseline (VAS rank)	23.00	26.13
Threatened – Vulnerable baseline (VAS rank)	26.18	22.67
Nervous – Anxious baseline (VAS rank)	25.20	23.74
Baseline cortisol	2.76 (1.28)	2.50 (1.55)
Extraversion (BFI - 44)	26.92 (5.80)	24.17 (6.04)
Agreeableness (BFI - 44)	34.56 (4.54)	33.91 (6.10)
Conscientiousness (BFI - 44)	32.88 (5.65)	33.48 (5.57)
Neuroticism (BFI - 44)	24.04 (6.30)	24.35 (6.26)
Openness (BFI - 44)	35.72 (4.60)	37.00 (4.91)
Self-esteem (Rosenberg)	20.20 (3.37)	20.48 (4.77)
Optimism (SSREIS)	41.84 (3.84)	40.65 (4.27)
Appraisal of emotions (SSREIS)	22.12 (3.71)	23.26 (2.78)
Utilisation of emotions (SSREIS)	14.56 (2.20)	14.91 (1.62)
Social skills (SSREIS)	18.60 (2.52)	19.17 (3.13)
Maternal care (PBI)	29.56 (6.14)	27.74 (5.77)
Maternal overprotection (PBI)	12.64 (7.23)	12.87 (7.66)

Figure 1. Study protocol

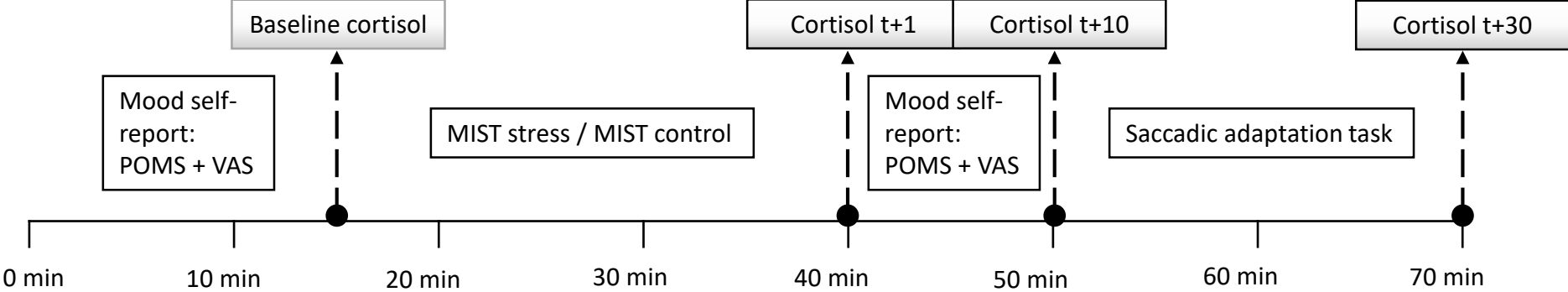


Figure 2. Saccadic adaptation task

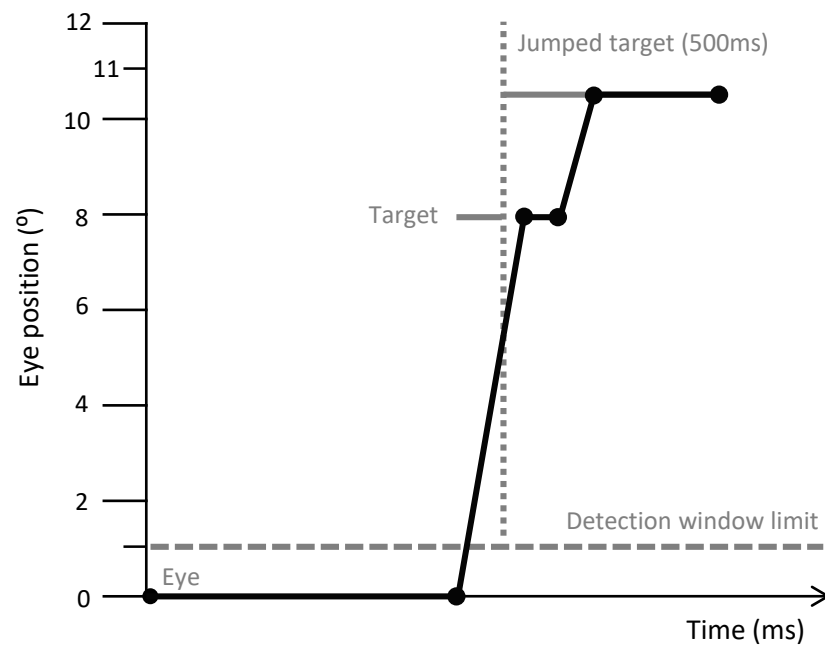


Figure 3A. Cortisol levels over time; **Figure 3B.** Total mood disturbance over time

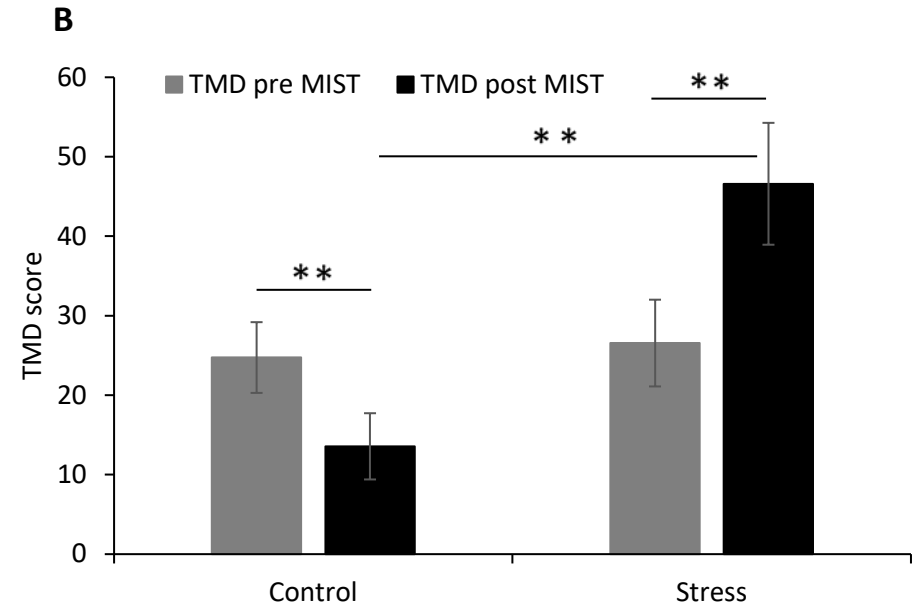
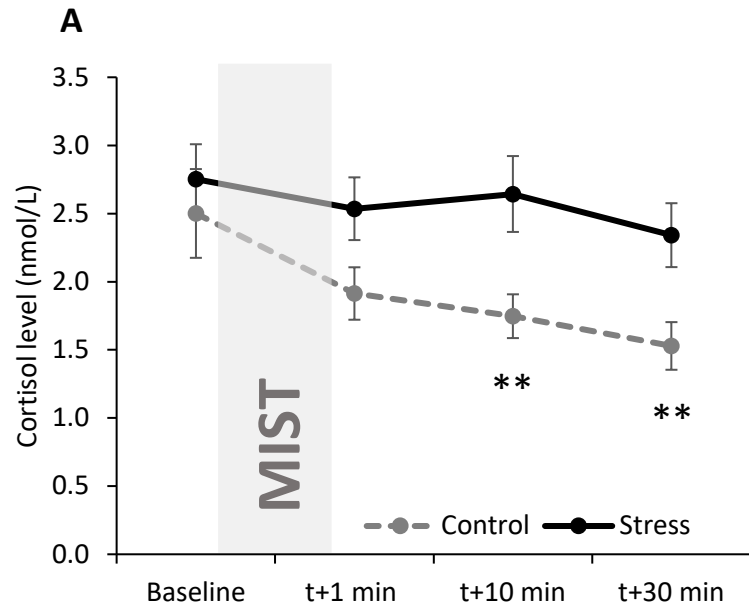


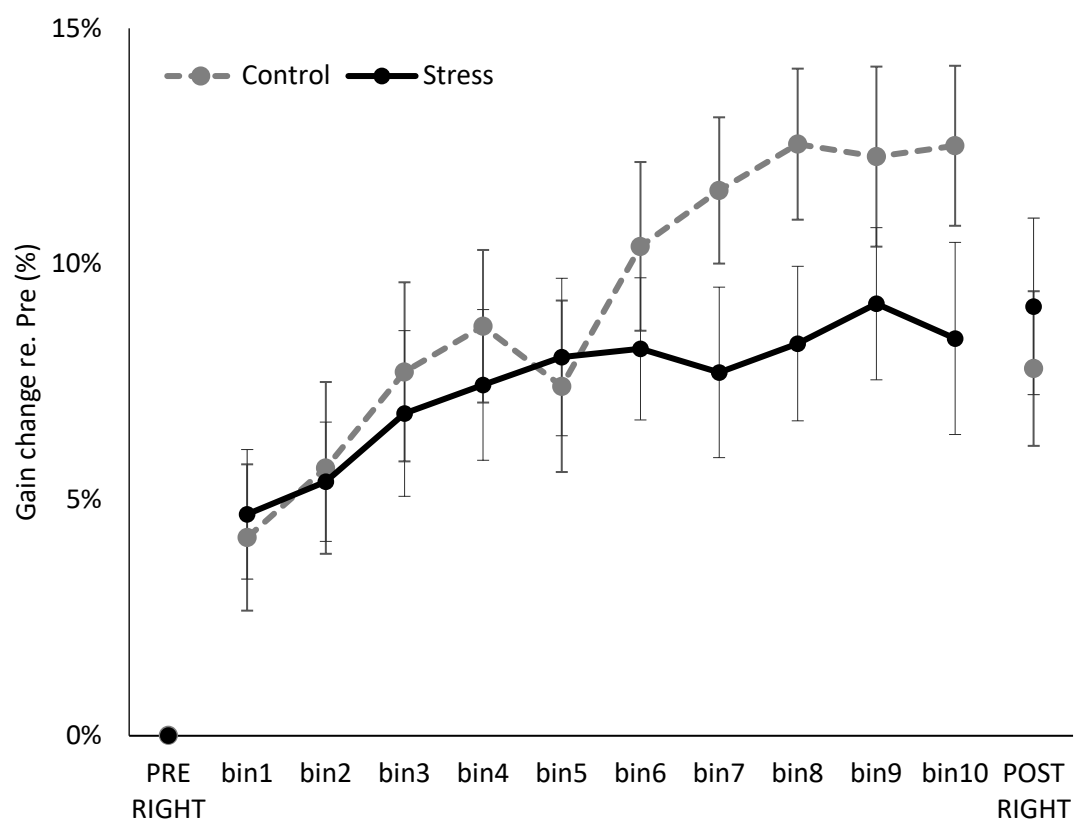
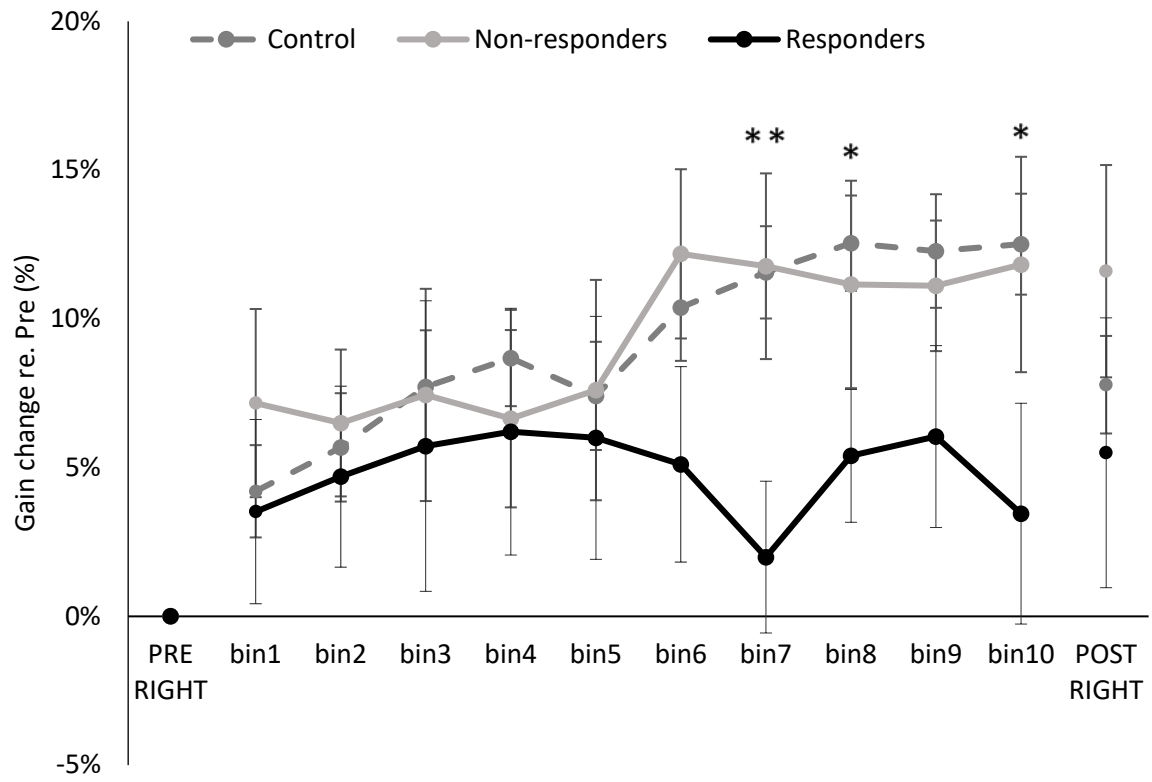
Figure 4. Gain change over time

Figure 5. Gain change over time in top and bottom cortisol responders



Supplemental methods:

Additional cortisol assessment information:

Cortisol was extracted by liquid chromatography with mass spectroscopy (LC-MS/MS). The lower limit of quantification (LLQ) for this method was determined as 0.8 nmol/L. There were 10 cortisol values below this limit (6 in the control group) in the pool of 196 samples. Here, non-detects were substituted with LLQ/2. This treatment method was shown to introduce fairly modest bias under certain conditions, which are met in the current sample, i.e., percentage of censoring <50% with log normal distributions and geometric standard deviations between 1.2 and 4 (1, 2).

Cortisol was collected approximately 10 minutes after the session began, which did not allow for potential pre-existing cortisol fluctuations to normalize across the sample. However, potential confounds were documented: within the prior hour before testing, none of the participants had engaged in any intense physical activity; sixteen participants reported caffeine consumption within the previous 12 hours; none of the participants had consumed alcohol or smoked twelve hours prior to the experiment; all reported being rested.

Supplemental results:

Associations between saccadic adaptation, stress and trait measures

There have been reports of associations between personality and stress reactivity e.g. (3). We therefore evaluated whether cortisol output and saccadic adaptation and subjective mood correlated with trait measures.

Agreeableness was positively associated with the total cortisol output (AUCg) at the level of the entire sample ($r = .304$, $p = .036$). This replicates the work by others found previously studies (4). Within each group separately, trait measures of personality, self-esteem, emotional intelligence and maternal bonding did not correlate significantly with AUCg.

Correlation analyses with trait measures also revealed that TMD post-MIST control was associated positively with measures of neuroticism ($r = .569$, $p = .005$). This correlation is also significant across groups ($r = .330$, $p = .022$). In the stress group, TMD post-MIST stress showed a negative correlation with the Maternal Care scale of the PBI ($r = -.446$, $p = .026$). This result is noteworthy as perceived quality of maternal care is associated with reduced cerebellar volume (5). Therefore traits related to prior interpersonal experiences may impact on stress reactivity following the psychosocial stressor.

The associations with saccadic adaptation are also of interest as they build on previous work discussing why the rate and magnitude of adaptation vary greatly across individuals (6, 7). We found in controls only, that the slope of adaptation positively correlated with openness to experience ($r = .473$, $p = .023$). Therefore, it could be argued that the more open you are to experience, the quicker you adapt, but only not when under stress. All other correlations between mood and measures of personality, self-esteem, emotional intelligence and maternal overprotection were not significant (Table S1 below). These exploratory associations should be regarded as tentative, and we urge caution until replicated given the small sample sizes. Nevertheless, we wanted to report these findings to motivate future replication studies.

In summary, stable personality traits such as agreeableness and neuroticism, as well as prior interpersonal experiences related to maternal care may impact on stress measures. Results vary within and across groups, suggesting caution when interpreting them.

Table S1. Correlations between trait measures and stress responsiveness

Control group															
	AUCg	TMD post-MIST	Adaptation slope	Extraversion	Agreeableness	Conscientiousness	Neuroticism	Openness	Self-Esteem	Maternal Care	Maternal Overprotection	Optimism	Appraisal of emotions	Utilization of emotions	Social skills
AUCg		.164	-.226	.124	.336	-.025	.076	-.220	.059	.072	-.152	.011	-.112	.401	.323
TMD post-MIST	.164		-.125	.040	.158	.203	.569**	-.153	-.275	.318	-.142	-.114	.090	.013	.150
Adaptation slope	-.226	-.125		.150	.063	.112	-.313	.480*	-.058	-.089	-.017	.256	.193	.275	-.148
Extraversion	.124	.040	.150		-.019	-.069	-.155	.455*	.240	.252	-.160	.615**	.030	-.063	.309
Agreeableness	.336	.158	.063	-.019		.449*	-.216	.009	.097	.347	.062	.138	.489*	.459*	.640**
Conscientiousness	-.025	.203	.112	-.069	.449*		.051	.090	-.156	.345	.056	-.163	.367	.030	.230
Neuroticism	.076	.569**	-.313	-.155	-.216	.051		-.275	-.516*	.317	-.080	-.476*	.159	.034	.066
Openness	-.220	-.153	.473*	.455*	.009	.090	-.275		.198	.335	-.183	.369	.223	.086	.107
Self-Esteem	.059	-.275	-.058	.240	.097	-.156	-.516*	.198		-.008	-.519*	.578**	-.459*	-.177	-.103
Maternal Care	.072	.318	-.089	.252	.347	.345	.317	.335	-.008		-.154	-.032	.412	.061	.411
Maternal Overprotection	-.152	-.142	-.160	.062	.056	-.080	-.183	-.519*	-.154			-.202	.191	.006	.352
Optimism	.011	-.114	.256	.615**	.138	-.163	-.476*	.369	.578**	-.032	-.202		-.195	-.051	.311
Appraisal of emotions	-.112	.090	.193	.030	.489*	.367	.159	.223	-.459*	.412	.191	-.195		.358	.511*
Utilization of emotions	.401	.013	-.063	.459*	.030	.034	.086	-.177	.061	.006		-.051	.358		.317
Social skills	.323	.150	-.148	.309	.640**	.230	.066	.107	-.103	.411	.352	.311	.511*	.317	
Stress group															
AUCg		.272	-.205	-.267	.280	.190	-.346	-.034	-.108	-.171	-.066	-.116	-.032	-.066	-.032
TMD post-MIST	.272		-.280	-.114	.060	.035	.331	-.119	-.324	-.446*	-.070	-.274	.378	.130	.193
Adaptation slope	-.205	-.280		-.062	.123	-.284	-.177	-.185	.175	.219	-.270	.258	-.060	-.238	.044
Extraversion	-.267	-.114	-.062		.285	.194	.181	.068	.216	.174	-.138	.192	.395	.242	.449*
Agreeableness	.280	.060	.123	.285		.550**	-.259	-.042	.519**	.196	-.559**	.415*	.238	-.141	.458*
Conscientiousness	.190	.035	-.284	.194	.550**		-.283	.326	.350	.092	-.219	.368	-.059	-.008	.286
Neuroticism	-.346	.331	-.177	.181	-.259	-.283		-.108	-.396	-.169	-.020	-.438*	.278	.143	.001
Openness	-.034	-.119	-.185	.068	-.042	.326	-.108		.044	.046	.187	.163	-.115	.193	-.050
Self-Esteem	-.108	-.324	.175	.216	.519**	.350	-.396	.044		.476*	-.459*	.551**	.061	-.117	.113
Maternal Care	-.171	-.446*	.219	.174	.196	.092	-.169	.046	.476*		-.270	.521**	.012	.121	.226
Maternal Overprotection	-.066	-.070	-.138	-.559**	-.219	-.020	.187	-.459*	-.270			-.388	-.324	.315	-.208
Optimism	-.116	-.274	.258	.192	.415*	.368	-.438*	.163	.551**	.521**	-.388		.335	.011	.433*
Appraisal of emotions	-.032	.378	-.060	.395	.238	-.059	.278	-.115	.061	.012	-.324	.335		.389	.683**
Utilization of emotions	-.066	.130	-.238	.242	-.141	-.008	.143	.193	-.117	.121	.315	.011	.389		.426*
Social skills	-.032	.193	.044	.449*	.458*	.286	.001	-.050	.113	.226	-.208	.433*	.683**	.426*	

Note. Correlations are presented separately for each group. * Correlation was significant at $p < .05$; ** Correlation was significant at $p < .01$

	AUCg	TMD post-MIST	Adaptation slope	Extraversion	Agreeableness	Conscientiousness	Neuroticism	Openness	Self-Esteem	Maternal Care	Maternal Overprotection	Optimism	Appraisal of emotions	Utilization of emotions	Social skills
AUCg		.342*	-.282	-.017	.304*	.076	-.163	-.151	-.030	-.019	-.104	-.009	-.110	.069	.100
TMD post-MIST	.342*		-.338*	.059	.107	.049	.330*	-.172	-.254	-.101	-.086	-.107	.175	.042	.093
Adaptation slope	-.288*	-													
Extraversion	-.017	.345*		-.043	.068	-.101	-.213	.128	.064	.046	-.149	.196	.075	-.034	-.011
Agreeableness	.304*	.107	.068	.124		.484**	-.234	-.021	.248	.278	-.206	.260	.327*	.132	.557**
Conscientiousness	.076	.049	-.101	.052	.484**		-.123	.215	.066	.197	-.084	.092	.120	.012	.259
Neuroticism	-.163	.330*		.011	-.234	-.123		-.185	-	.051	-.049	-.455**	.228	.100	.038
Openness	-.151	-.172	.128	.222	-.021	.215	-.185		.455**	.136	.159	.001	.244	.051	.156
Self-Esteem	-.030	-.254	.064	.213	.248	.066	-.455**	.136		.198	-.488**	.551**	-.177	-.135	-.017
Maternal Care	-.019	-.101	.046	.238	.278	.197	.051	.159	.198		-.214	.266	.136	.081	.297*
Maternal Overprotection	-.104	-.086		-.148	-.206	-.084	-.049	.001	-	-.214		-.290*	-.101	.184	.099
Optimism	-.009	-.107	.196	.429**	.260	.092	-.455**	.244	.551**	.266	-.290*		.075	-.028	.343*
Appraisal of emotions	-.110	.175	.189	.327*	.120	.228	.051	-.177	-.136	-.101		.075		.387**	.591**
Utilization of emotions	.069	.042	.075	.089	.132	.012	.100	.156	-.135	.081	.184	-.028	.387**		.370**
Social skills	.100	.093	-.034	.335*	.557**	.259	.038	.049	-.017	.297*	.099	.343*	.591**	.370**	

Note. Correlations are presented across both groups. * Correlation was significant at $p < .05$; ** Correlation was significant at $p < .01$

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