



## Psychosocial stress affects the acquisition of cerebellar-dependent sensorimotor adaptation

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### 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 min after the MIST. Saccadic adaptation was assessed approximately 10 min 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.

### 1. 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

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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 (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 stress process, 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, 1966a, b), 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.

**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 <sup>Δ</sup>	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)

Note. 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. Unless otherwise specified, numbers depict group averages followed by SD in brackets. ▲VAS data shows mean ranks. ΔCycle phase could not be established for one participant due to reported amenorrhoea.

## 2. Materials and methods

### 2.1. 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 18–34 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 amenorrhoea (no menstrual cycle) was established for one participant due to contraception. All participants reported having had a good night's sleep (7–8 h). Within the hour before testing, none had engaged in any

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