

Large-scale Resting-State Network Dynamics Under Acute Stress

Master Thesis Cognitive Neuroscience

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Abstract

An adaptive response to stressors requires the dynamic regulation of cognitive resources. Animal research shows distinct roles of the physiological hormone cascades involved in the stress response and their spatial-temporal dynamics. The spatial-temporal profile of neural functioning under stress form core nodes in multiple large-scale networks. The aggregation of both animal and human studies has therefore resulted in a model of how these large-scale networks respond to stress, which is postulated to entail the dynamic allocation of processing resources between the *Saliency*, *Executive Control*, and *Default Mode* Networks. Here, we test this model using resting state fMRI by contrasting the functional connectivity profiles of these networks after stress induction using the *socially evaluated cold pressor task* (SECPT) and control conditions in a population of first year (bio-) medical students. We additionally assess whether individualized stress reactivity, as determined by the HPA axis stress response, impacts shifts in these networks after acute stress. The results show decreased functional connectivity of the *Executive Control* and *Default Mode* Network with distinct subregions of the cerebellum after stress. No effects of HPA response on these dynamics were found. Our results demonstrate the importance of cerebellar contributions to large-scale network investigations and their functional role in the adaptive stress-response.

A fundamental component of survival is the ability to adapt to new challenges that may arise in an organism's environment. A series of biological mechanisms have evolved to support adaptation to change and maximize the likelihood of survival. These include a complex interplay of stress systems that, when prompted, allow us to respond adequately to threatening events and return to equilibrium when the challenge is dealt with. While the nature of stressful events has changed with the development of modern societies, these systems serve us in the same manner for a big presentation at work, as they did when confronted with a dangerous predator while out on a hunt. The inner-workings of stress-systems have been of great interest to scientific investigations since the pioneering work of Walter Cannon (fight-or-flight; Cannon, 1915) and Hans Selye (General adaptation

syndrome; Selye, 1936, 1976) and remains an active field of research today. Related psychopathologies such as mood and anxiety disorders are estimated to be the main source of mental health-related disease burden worldwide (Patel et al., 2016), underlining the importance of an accurate understanding of how these systems function in health and disease.

Stress can be described as a physiological and psychological offset from homeostasis (Cannon, 1929). Any event that threatens or is perceived to threaten homeostasis is referred to as a 'stressor' (de Kloet, Joëls, & Holsboer, 2005). The stress concept, therefore, entails the reciprocal interaction between external events and the internal state of an organism. Importantly, stressors elicit physiological and psychological changes that allow an organism to adaptively cope with the challenge imposed. To accomplish this, multiple hormone cascades are put into action and cognitive functions are dynamically up- or downregulated.

On a physiological level, changes in the homeostatic system are linked to multiple pathways that support the stress response with different temporal and spatial effects (Hermans, Henckens, Joëls, & Fernández, 2014). These include the sympatho-adrenomedullary axis (SAM-axis; Piazza, Alemeida, Dmitrieva, & Klein, 2010; Russel & Lightman, 2019) and the hypothalamic-pituitary-adrenal axis (HPA-axis; Russel & Lightman, 2019). Both systems are responsible for the release of hormones that are involved in the stress response, including catecholamines (e.g norepinephrine) and corticosteroids (e.g cortisol), respectively. In the initial phase of the stress response, activation of the locus coeruleus in the brainstem causes the release of norepinephrine in the brain (Rajkowski, Kubiak, Ivanova, & Aston-Jones, 1998; Valentino & van Bockstaele, 2008). Peripherally, norepinephrine is released from the medulla of the adrenal gland into the bloodstream (Mason, 1968), which is initiated by the SAM-axis. The actions of this initial surge of catecholamines starts instantaneously with the onset of stress and typically normalize within 30 minutes after stress-onset (Joëls, Fernandez, & Roozendaal 2011). These actions, therefore, allow us to respond to the immediate demands that a stressor puts on us.

The HPA-axis, on the other hand, asserts its effects later. It does so by initiating the release of corticosteroids such as cortisol (Russel & Lightman, 2019). Concentrations of cortisol peak

between 20 to 30 minutes after stress onset (Kirschbaum, Bartussek, & Strasburger, 1992). This timing of the cortisol response suggests that the window of action lies primarily outside of the immediate stress response. The final effects of corticosteroids constitute actions at the level of gene expression where they act as transcription factors (Joëls, Sarabdjitsingh, & Karst, 2012; Russel & Lightman, 2019). These alter the transcription of genes to either increase or decrease the levels of proteins in the neuron and thereby affect neural functioning. Because corticosteroids must travel further into the cell nucleus for these actions to take effect, this process typically takes at least one hour to be initiated but is also longer lasting (Meijer, Buurstedde, & Schaaf, 2019). The genomic actions of glucocorticoids also differ widely between areas of the brain (Meijer et al., 2019). Besides these long-term effects, corticosteroids also act on membrane-bound receptors where they assert effects on a quicker timescale (Meijer et al., 2019). Therefore, corticosteroids have both rapid and slower modes of action, mediated by different corticoid receptor types (Meijer et al., 2019).

Earlier animal experiments have shed light on how these stress hormones affect neural functioning in specific brain regions. For example, the large amounts of noradrenaline availability associated with the stress response leads to activation of different receptors in the prefrontal cortex (PFC) and the amygdala (Birnbaum, Gobeske, Auerbach, Taylor, & Arnsten, 1999; Arnsten, 2009; Abraham et al., 2008; Hermans et al., 2011). A similar pattern has been observed for dopaminergic activity in the same areas, either decreasing or increasing neural activity respectively (Vijayraghavan et al., 2007; Lamont & Kokkinidis, 1998). This suggests that catecholaminergic activity in the stress-response is region-specific and may exert oppositional effects in these regions. Corticosteroids act in this manner as well: Neuronal excitability of the basolateral amygdala has been found to be enhanced by stress level glucocorticoids (Karst et al., 2010; Duvarci & Paré, 2007) while in the PFC, corticosteroids exert different effects over time. Fast corticosteroid actions potentiate the downregulatory effects of noradrenaline in the PFC (Barsegyan, Mackenzie, Kurose, McGaugh, & Roozendaal, 2010) while the slow actions of corticosteroids enhance PFC functioning (Yuen et al., 2009), thereby possibly reversing the rapid effects of catecholamines and corticosteroids.

Thus, stress-related ligands seem to initially enhance amygdala function, while impairing PFC

function. Taking the temporal dynamics of these ligands into consideration shows an interesting pattern as well: slow corticoid actions seem to oppose the rapid effects of catecholamines and corticosteroids (Hermans et al., 2014). Such oppositional effects of the early and late processes of the stress response might therefore be an important mechanism for adaptive recovery after stress (De Kloet et al., 2005).

Importantly, these two systems (SAM and HPA axes) do not merely act on their own. Corticosteroid and catecholaminergic actions interact at multiple sites in the brain to potentiate each other's actions (Roozendaal, Williams, & McGaugh, 1999; Saal, Dong, Bonci, & Malenka 2003). In the rat prefrontal cortex, corticosteroids interact with noradrenaline to enhance memory consolidation and impair working memory (Barsegyan et al., 2010; Roozendaal, McEwen, & Chattarji, 2009). In the amygdala, corticosteroid administration increases levels of noradrenaline 15 minutes post-administration which increases hippocampal plasticity and memory consolidation (McCreynolds et al., 2010). It is therefore likely that the immediate effects stress has on cognition and behavior are in part modulated by an interplay between catecholamines and the fast acting corticosteroids.

On a cognitive level, stress affects attention, memory, and executive functions. The change in norepinephrine tone increases salience detection and shifts focused attention towards greater 'global scanning' of the environment (Rajkowski et al., 1998; Aston-Jones & Cohen, 2005). Memory, here, is affected in multiple ways (Schwabe, Joëls, Roozendaal, Wolf, & Oitzl, 2012). While cortisol-norepinephrine interactions enhance consolidation (Barsegyan et al., 2010), they also impair the retrieval of long-term memories (Roozendaal, Hahn, Nathan, Quervin, & McGaugh, 2004). Acute stress also impairs executive functions such as *complex reasoning, focusing attention, and working memory* (Arnsten, 2009). As stress subsides, cognition returns to baseline. This stage of the stress-response is referred to as the *recovery phase* and is hypothesized to be functionally related to the downstream (genetic) actions of glucocorticoids (De Kloet et al., 2005).

This dynamic shift in cognitive functioning occurs in cognitive domains that are supported by distinct large-scale networks; collections of regions that systematically co-activate and deactivate and are functionally connected (Bressler & Menon, 2010). The aforementioned

brain regions affected by stress form core nodes in two of such large-scale networks. Specifically, the PFC is an important node in the Executive Control Network (ECN), together with the posterior parietal cortex (PPC) and is functionally related to executive functions (Bressler & Menon, 2010). The amygdala is a constituent part of the Salience network (SN), together with the insula and the anterior cingulate cortex (ACC) and is functionally related to salience detection (Seeley et al., 2007). It is therefore plausible that stress induced changes take place at the level of these large-scale networks.

The handful of imaging studies investigating changes in large-scale network functional connectivity (FC) induced by stress support this notion. Stress induction has been shown to increase SN FC at the expense of ECN FC (Hermans et al., 2011, 2014; Young et al., 2017). This upregulation of the SN appears to be sensitive specifically to adrenaline, and not cortisol. Although cortisol levels correlated with increasing SN functional connectivity, pharmacological blockage of cortisol receptors did not reduce SN upregulation, while noradrenaline blockade did (Hermans et al., 2011). Chronic stress decreases functional coupling between the dorsolateral prefrontal cortex (DLPFC) and the PPC, which are both core nodes in the ECN (Liston, McEwen, & Casey, 2008). A third network of interest is the Default Mode Network (DMN). The DMN is intrinsically linked to both the ECN and SN, is implicated in stress-related disorders (Whitfield-Gabrieli & Ford, 2012), and has been observed to be affected as a function of arousal (Young et al., 2017).

These stress-induced shifts in network connectivity have been observed under task conditions, which skews the observed changes towards the SN and ECN, as they are increasingly involved in meeting task demands (Dosenbach et al., 2007). The DMN, on the other hand, is functionally related to mind-wandering, self-reflection, and mental time travel—such as thinking about past events or envisioning the future (Whitfield-Gabrieli & Ford, 2012). When interacting with external stimuli during attention-demanding tasks, the DMN is suppressed. Therefore, the DMN and ECN are often observed to be anticorrelated (Whitfield-Gabrieli & Ford, 2012). Thus, it could be possible that stress-induced network dynamics look differently under rest conditions. One study has tested this by contrasting resting-state activity of the three networks before stress induction, and 20 minutes after stress induction (Zhang et al., 2019). They found that SN functional connectivity was

increased while the DMN showed a decrease in functional connectivity. Moreover, SN activity increased as a function of the stress-induced cortisol rise and the reduction in both *local* (within-network) and *global* (whole-brain) synchronization of the DMN correlated with individual cortisol responses, although this correlation was relatively low. Interestingly, no changes in ECN functional connectivity were found. These results indicate that a similar, but distinct network reorganization occurs in response to stress under rest conditions during the time window where cortisol levels are at their peak. Another study looked at resting-state connectivity in these three networks before and after a mild social stressor and found increased connectivity of the DMN with SN nodes (Clemens et al., 2017). This suggests that DMN functioning is altered to allow for effective salience detection, in this context. However, none of these previous studies have contrasted these findings with similar (resting-state) network connectivity changes, without stress induction prior to data acquisition.

These previous findings have been consolidated into model that aims at explaining stress reactivity and recovery at the level of large-scale networks and the relationship with stress-related catecholamine and corticosteroid actions (Hermans et al., 2014). In this model, the SN is upregulated in the acute phase while the ECN is concurrently downregulated. This initial shift in network dynamics is thought to be under the control of the fast actions of catecholamines and non-genomic corticosteroid actions. In the later recovery phase, this shift is reversed—as the SN is downregulated and the ECN upregulated—an effect which is thought to be under the control of late non-genomic and genomic effects of corticosteroids. Dynamic reallocation of processing resources between these networks has been hypothesized to underlie this network shift.

The current study aims to test the acute changes in large-scale resting-state network activity after a stress- and non-stress induction procedure in two separate sessions in healthy participants and the modulatory role herein of the cortisol response. In line with previous research, the hypotheses are to find increased Salience Network connectivity after stress induction relative to control, decreased connectivity within the Default mode network, and increased connectivity with Salience Network nodes. Relative to control conditions, no changes in Executive Control Network functional connectivity after stress induction are

expected. Individual cortisol responses characterized by HPA-axis sensitivity to stress-induction are expected to be related to connectivity changes of the Salience and Default Mode Network.

Characterization of the stress response in terms of large-scale network dynamics may aid in investigating altered brain functioning in stress-related psychopathology and in the design, development, and evaluation of interventions that affect large-scale network dynamics, such as mindfulness-based stress reduction (Kilpatrick et al., 2011; Kral et al., 2018) and neurofeedback-based interventions (Chiba et al., 2019).

Methods

Participants

A total of 84 participants were recruited for the study “Stress resilience and the Brain in Medical Students”, of which 53 (39 females, 14 males) aged 17-25 ($M = 19$, $SD = 2$) with complete MRI scans are reported. Twenty of the female participants declared use of hormonal contraceptives. All participants were first-year students of the Medicine or Biomedical Sciences bachelor programs, at the Radboud University in Nijmegen, the Netherlands. Participants were right-handed with normal or corrected-to-normal vision and were native Dutch speakers. Written consent was provided by each participant before the start of the experiment, followed by an MRI screening form. Participants were compensated with a total of 160 euros for their participation in this study. The project protocol (‘Large-Scale Network balance and Daily Life Stress Reactivity’) was approved by the local ethics committee (CMO Nijmegen/Arnhem, The Netherlands).

Procedure

General setup

In anticipation of the two scheduled fMRI sessions, participants completed two separate weeks of Ecological Momentary Assessment (EMA). One of these weeks was a regular week (‘*Control week*’) and the other was a week before an exam (‘*Stress week*’). In each week, participants took two saliva samples at home, one at the beginning and one at the end of the week; both samples were taken around noon, before consuming food. At the end of each week, participants visited the testing center for behavioral testing.

For scanner-naïve participants, a separate session was planned where a T1 anatomical image was acquired, prior to the fMRI sessions. This was done in accordance with previous evidence, which suggests that novel exposure to MRI scanning is linked to increased cortisol levels (Tesner, Walker, Hochman, & Hamann, 2006).

This was followed by two separate counterbalanced fMRI sessions. In one session, the participants performed a stress induction task prior to scanning (stress session) while in the other, they performed a similar control procedure (control session; see *stress induction procedure*). Participants with prior MRI experiences undertook the anatomical scan at the end of their first fMRI session. Participants performed multiple interleaved tasks and resting-state blocks during the functional sessions, of which one resting-state block is discussed here (Figure 1). The EMA data, behavioral data, task data, and other resting-state data are beyond the scope of this thesis and will not be further discussed.

Testing took place between 10:00 and 16:00 on weekdays and/or weekends. Participants were invited to the testing center 2 hours before the start of the MRI session to allow cortisol levels to return to baseline, and to allow participants to practice the tasks within this protocol. At the start of the fMRI sessions, participants were instructed to remove their left shoe and sock for the first tasks, and instructed that their task involved putting their foot in water (see *stress induction procedure* below). After placing the subjects on the scanner bed, the first saliva sample was taken followed by the stress induction or control procedure. A second saliva sample was taken upon completion of this procedure. Subjects were then placed inside the scanner where they performed the tasks (see *fMRI procedure*) and collected three additional saliva samples.

Stress induction

Participants underwent a modified version of the *Socially Evaluated Cold Pressor Task* (SECPT) before the start of fMRI scanning. This procedure combines a physical, mental, and social stressor as a robust and reliable way to induce a stress response in an experimental setting (Schwabe & Schächinger, 2018).

The procedure was as follows: An experimenter with whom the participants never had contact with (i.e. the stressor) entered the scanner room and placed a box filled with ice water set to 2°C next to the scanner bed. Participants were informed that their foot would be placed in the water for three minutes, but they could indicate to have their foot removed earlier if it becomes unbearable. Afterward, their foot was wrapped in a towel and placed back on the scanner bed. Participants then performed a difficult arithmetic task for another three minutes, although they were not informed of this set duration here. In this task, they are instructed to count back from the number '1872' in steps of 17. If participants were too slow (> 6 seconds to a response), they were instructed to speed up. If they made a mistake, they were instructed to start from the beginning. Two consecutive time-outs prompted the instruction to start over as well. The experimenter maintained a neutral facial expression and tone throughout the procedure and provided no feedback outside of the responses to wrong or untimely answers.

A similar task setup was used for the control procedure, with a few changes. The ice water was replaced with room temperature tap water. Instead of the difficult arithmetic task, participants were instructed to count upward from zero, in steps of five. Mistakes were not corrected, and the procedure was performed by a familiar experimenter.

Saliva sampling

Five saliva samples were collected during each of the fMRI sessions. Sample one (S1) was taken before the stress induction or control procedure (M = -5 minutes, SD = 3 minutes). The second sample (S2) was taken immediately afterward (M = 8 minutes, SD = 4 minutes). The third sample (S3) was taken around the peak cortisol time after the start of the stress induction or control procedure (M = 37 minutes, SD = 6 minutes). The fourth sample (S4) was then taken during the scanning break, approximately one and a half hours after the initial stress- or control procedure (M = 89 minutes, SD = 10 minutes) with the last sample (S5) taken at the end of the session, approximately two and a half hours post-stress induction or control procedure (M = 153 minutes, SD = 9 minutes).

The first three samples were taken while the participants laid supine in the scanner. The experimenter placed the cotton swab inside their mouths and instructed the participants to

keep it inside of their mouths, without chewing on it, for three minutes. The last two samples were taken by the participants themselves. Participants were instructed to place the cotton swab inside of their mouth, without touching it with their fingers. Samples were then stored on-site in a -80°C freezer until analysis. The content analysis of the samples was performed by Dresden LabService GmbH (Dresden, Germany).

fMRI procedure

Each of the two fMRI sessions were divided into an identical *early* and *late* run, matching the temporal dynamics of the stress response. In between the two runs participants were removed from the scanner for a short break. The runs each consisted of three tasks blocks intermixed with 2 resting state runs. The task blocks were made up of three tasks each designed to engage one of the three networks of interest (DMN, SN, and ECN). Task data is not considered in this thesis; therefore, a detailed description of these tasks is not provided.

Participants were provided written instructions prior to the resting state run on screen. Subjects were instructed to fixate on the cross, not to think and just 'let their mind wander' for the next five minutes. A flow chart of the scanning session is presented in figure 1.

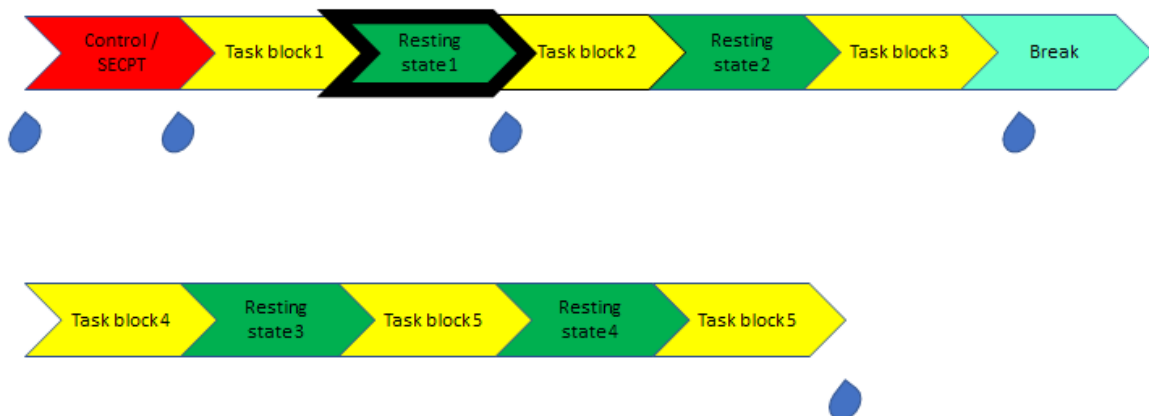


Figure 1: Diagram showing the setup of the MRI sessions. Droplets represent moments where saliva samples were taken. The black outlined block represents the data of interest in the current study.

Data acquisition

MRI scan acquisition

MRI scans were acquired using 3T Prisma and PrismaFit scanners (Siemens AG, Healthcare Sector, Erlangen, Germany) with a 32-channel head coil. Subjects were placed inside the bore in a head-first supine position. Their heads were secured with a pillow and tape was placed over their foreheads to reduce head movements. Heart rate, respiration, and skin conductance were measured during the functional sessions for subsequent noise reduction in the functional images.

A 5-minute Magnetization-Prepared Rapid Gradient Echo (MP-RAGE) sequence was used to acquire 1-millimeter T1-weighted anatomical images. The sequence consisted of the following set of parameters: TR/TI/TE=2300/1100/3ms, 8° flip angle. The acquired images have a 1x1x1 millimeter isotropic spatial resolution, resulting in a 256x216x176 matrix size. Parallel imaging (iPAT = 2) was used to accelerate the acquisition time and reduce susceptibility artifacts (Poser, Versluis, Hoogduin, & Norris, 2006).

The functional images were acquired using a MultiBand 3 MultiEcho3 sequence (TR/TE₁₋₃=1500/13.4/34.8/56.2ms, 75° flip angle) which allows for better imaging of deeper gray matter regions and regions close to air-tissue boundaries that have a relatively shorter T2* (Poser et al., 2006). These T2*-weighted images have a 2.5x2.5x2.5 millimeter isotropic resolution (84x84x84 matrix size). Parallel imaging (MB=3; iPAT=2; PF=7/8) was used for the same reasons as the anatomical sequence.

Data analysis

HPA-axis sensitivity

The cortisol stress response was calculated similarly to Henckens et al. (2016). In the current study, participants took two samples at home during the EMA weeks at noon before consuming food. Therefore, we determine basal cortisol levels as the average of the two samples taken during the EMA control week. Cortisol levels peak around ~30 minutes after administration of a stressor (Kirschbaum, Bartussek, & Strasburger, 1992), therefore the third sample was taken around this time point during fMRI sessions. Thus, the third sample (S3) of each of the fMRI sessions was used as the peak cortisol measure for the stress and control sessions. The cortisol stress response in the current study is calculated using the following formula:

$$\text{HPA Index} = \frac{\text{Cortisol level stress session (S3)} - \text{Cortisol level control session (S3)}}{\text{Mean Basal cortisol level (2 samples measured at home)}}$$

This results in a single score for each participant that reflects HPA-axis sensitivity to the stress induction procedure, which is normalized to baseline cortisol levels. Two participants who were missing a stress or control session sample had their HPA Index set to 0. One participant was missing one of the basal level samples, and had it calculated using the single sample that was present.

Stress induction

To test whether the stress induction procedure was successful, a within-subject mixed-effects model was utilized to test the peak versus peak difference between the stress and control session salivary cortisol levels. Contraceptive use was added to the model as a fixed-effects factor to control for hormonal contraceptive modulation of the stress-induced cortisol response (Nielsen, Segal, Worden, Yim, & Cahill, 2012).

MRI preprocessing

The T1-weighted anatomical images were skull-stripped with the Brain Extraction Tool (Smith, 2002). The three echoes of the functional volumes are combined using PAID weighting (Poser et al., 2006; Posse, 2012), where 30 volumes were used for the weighting calculation. Images were initially processed with MELODIC (Beckman & Smith, 2005) and registration parameters were derived. Specifically, the T1 was registered to standard space, and the functional image was registered to the registered T1. The denoised images for each participant were then registered into MNI152 standard space. Low-frequency drifts are removed by the application of a high-pass filter (cut-off at 100 seconds). Motion related artifacts were identified with the use of ICA-based Automatic Removal Of Motion Artifacts (ICA-AROMA; Pruim, Mennes, Rooij, Llera, Buitelaar, Beckmann, 2015), which selects motion-related components from a set of independent components estimated by MELODIC.

Statistical analysis

The contrasts include the session differences (stress>control and control>stress) in each of the brain networks of interest (DMN, SN, and ECN). These were analyzed using a multisubject multisession group ICA with dual regression (Nickerson, Smith, Öngür, & Beckman, 2017; Beckman, Mackay, Filippini, & Smith, 2009).

MELODIC with multi-session temporal concatenation was used on the AROMA-cleaned data to estimate independent components (ICNs). The number of estimated ICNs was limited to the first 25 independent group-level components. This set of ICNs were then compared to the FIND templates (Shirer, Ryali, Rykhlevskaia, Menon, & Greicius, 2012) of the three networks of interest by calculating the Dice similarity coefficients (Dice, 1945) between ICNs and templates. These templates included the left and right ECN, dorsal and ventral DMN, and the SN, for a total of five network components that were included in subsequent analysis. The components with the highest DSC for one of the networks were selected to represent each of the networks.

A dual regression analysis was performed to extract subject-specific network components for each stress and control session separately (Beckman, Mackay, Filippini, & Smith, 2009). First, timeseries were extracted for each of the five group-level ICNs for each subject in each session. Second, subject-specific statistical maps for each group-level ICN were extracted for both sessions. The statistical maps were then subtracted from each other in both directions, resulting in stress > control and control > stress contrast maps for each participant, in each of the networks. Finally, the individual subject maps were concatenated into a single 4D file for each network and contrast.

A one-sample T-test was then conducted on each contrast image for a total of 10 independent tests (5 networks x 2 contrasts) to test for differences within each network between the stress and control session. These tests were conducted via permutation using the randomise tool in FSL (Winkler, Ridgeway, Webster, Smith, & Nichols, 2014) with Threshold-Free Cluster Enhancement (TFCE) and Family-Wise Error (FWE) correction for multiple comparisons. HPA indices of each participant were added as a parametric modulator, to test network modulation by the HPA-axis sensitivity using f-tests.

Results

Cortisol response

Analysis of salivary cortisol samples confirmed successful stress induction (figure 2). Linear mixed model analysis with *session* and *contraceptive use* as fixed effects factors, and subjects as random effect factor showed a significant session difference at peak cortisol time ($t_{S3} = 2.19, p = 0.033$). Hormonal contraceptive use had a significant effect on peak cortisol levels ($t = 2.09, p = 0.04$). None of the remaining sampling times (S1, S2, S4 and S5) showed a significant difference between the two sessions ($t_{S1} = -1.4, p = .17$; $t_{S2} = -1.59, p = .12$; $t_{S4} = 1.86, p = .07$; $t_{S5} = 1.31, p = .2$)

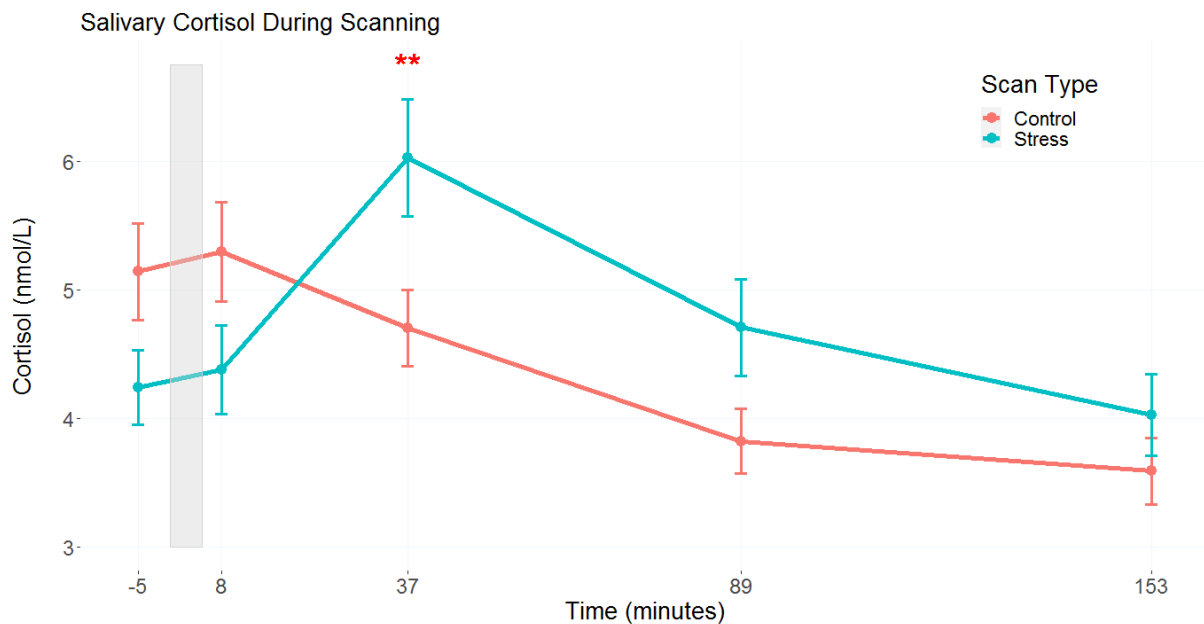


Figure 2: Salivary cortisol response during the control (red) and stress (blue) sessions. Shaded area indicates when the stress or control procedure occurred. Time is in minutes relative to the start of the procedures, averaged over participants. ** $p < .05$.

Network selection

Independent components of interest were selected by comparing the corresponding FIND template to each of the 25 group-level ICNs estimated by MELODIC ICA decomposition. The components with the highest overlap with the left ECN (DICE = 0,38), right ECN (DICE =

0,28), dorsal DMN (DICE = 0,44), ventral DMN (DICE = 0,35), and SN (DICE = 0,43) templates were selected for further analysis. All the selected network templates contained core nodes that are typically associated with that network (Figure 3). The core regions of each network are reported in table 1.

Table 1: Overview of core network areas in the group ICNs of the SN (Salience Network), ECN (Executive Control Network), and DMN (Default Mode Network).

Network	Region	MNI coordinates
SN	bilateral insula	(-)39 11 0
	bilateral anterior cingulate cortex	(-)1.8 20 30
ECN - Right	right dorsolateral prefrontal cortex	31 56 15
	right posterior parietal cortex	51 -45 44
ECN - Left	left dorsolateral prefrontal cortex	-31 56 15
	left posterior parietal cortex	-51 -45 44
DMN - Dorsal	posterior cingulate cortex	0 -49 30
	medial prefrontal cortex	-1 42 -15
	bilateral parahippocampal gyrus	(-)28 -32 -18.5
	bilateral hippocampi	(-)25 -14 -21
	bilateral medial temporal gyrus	(-)58 -9 -14
	bilateral precuneus	(-)2 -59 37
DMN - Ventral	medial prefrontal cortex (inc. anterior cingulate cortex, paracingulate cortex, and frontal poles)	(-)0.5 48 10
	Posterior cingulate cortex	2.5 -23.5 41

Each group level ICN map contained multiple areas not typically associated as core nodes to the network. Other areas present in the SN group template were the frontal pole, superior frontal gyrus, supramarginal gyrus, and cerebellum. Other areas in the right ECN included the right middle and inferior temporal gyri, right paracingulate gyrus, right angular gyrus, right caudate, right posterior cingulate cortex, right superior lateral occipital cortex, and the left cerebellum. The left ECN contained the right middle and inferior temporal gyri, posterior cingulate cortex, left caudate, and the right cerebellum in addition to its core components. Other areas included in the dorsal DMN were the bilateral lateral occipital gyrus, and the cerebellum. The ventral DMN contained the bilateral caudate, left accumbens, and bilateral insula in addition to its core components.

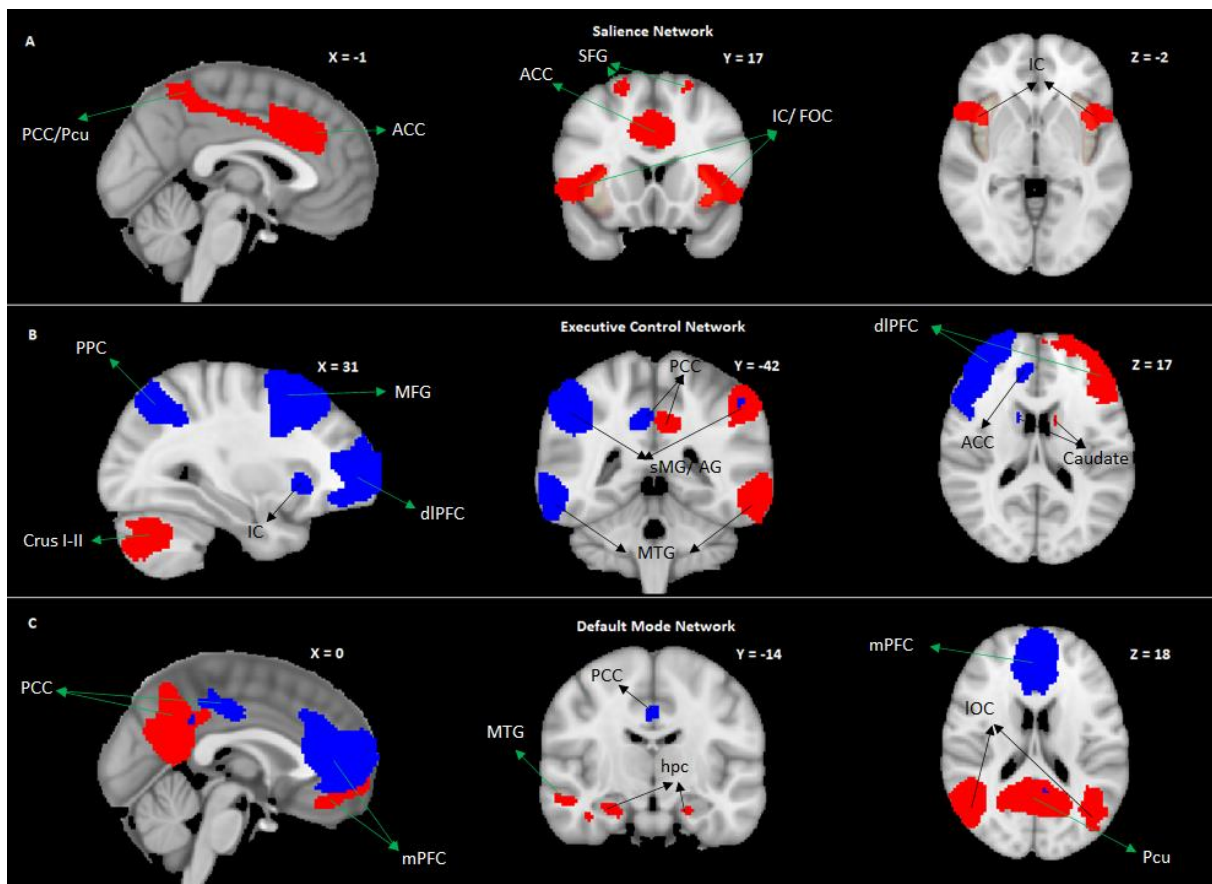


Figure 3: SN (Salience Network) – ECN (Executive Control Network): Right (Blue) and Left (Red) divisions – DMN (Default Mode Network): Ventral (Blue) and Dorsal (Red) divisions. As derived ICA group templates in MNI152 standard space. PCC: posterior cingulate cortex, mPFC: medial prefrontal cortex, Hpc: hippocampus, IOC: lateral occipital cortex, Pcu: precuneus, dIPFC: dorsolateral prefrontal cortex, PPC: posterior parietal cortex,

MFG: middle frontal gyrus, SFG: Superior frontal gyrus, MTG: middle temporal gyrus, sMG: supramarginal gyrus, AG: angular gyrus, ACC: anterior cingulate cortex, IC: insular cortex, FOC: frontal operculum cortex

Session differences

Group level session comparison showed significant changes in connectivity in several of the networks under acute stress. For the contrast of control>stress, there was greater functional connectivity (FC) in the left ECN with the left cerebellum during the control session (figure 3A). Increased FC was observed with the right cerebellum (lobule IX and Crus II, $p < 0.01$, uncorrected), however, these clusters did not survive multiple correction. For the same contrast, greater FC was observed between the right ECN and a cluster in the right cerebellum (Crus I and II), while the stress>control contrast revealed greater FC with a small cluster in the left cerebellum (lobule VIIb-crus II). No HPA axis modulation of functional connectivity was observed in the right or left ECN.

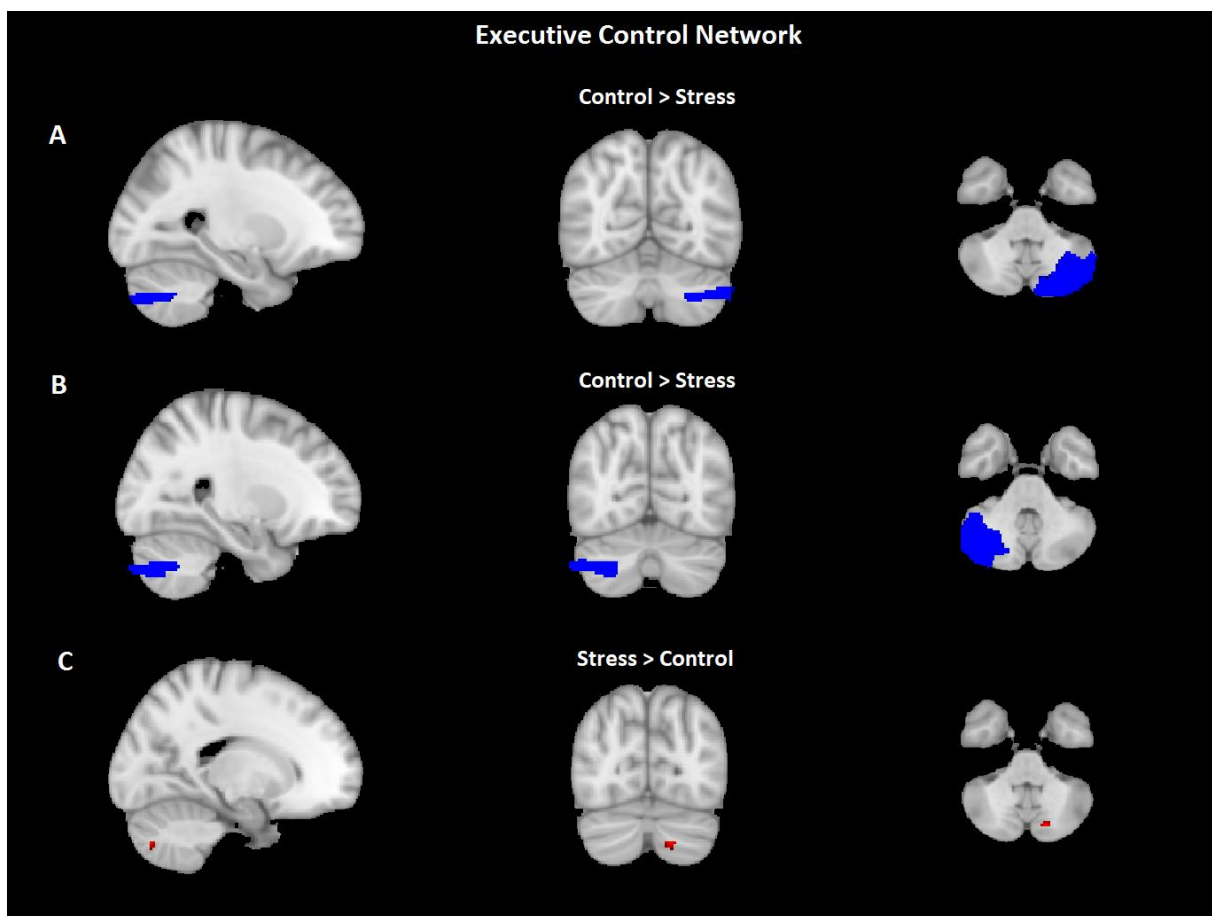


Figure 4: Decreased connectivity (blue) between the left Executive Control Network and the left Cerebellum (A). Decreased connectivity was found between the right Executive Control Network the right Cerebellum (B)

while increased connectivity (red) was found with a small cluster in the left Cerebellum (C).

A significant lower FC was observed between the ventral DMN and bilateral cerebellum (Crus I and lobule IX) in the *stress* session with respect to the *control* session, as seen as greater FC in these areas for the *control*>*stress* contrast. Within the dorsal DMN, a significant difference was observed in the posterior cingulate cortex/precuneus, as well as with the bilateral Crus II of the cerebellum (Figure 4B) for the same contrast. A HPA axis modulated difference was observed in the right frontal pole and left cerebellum, ($p < .01$, uncorrected) however, this did not survive correction for multiple comparisons.

Stress-induced upregulated SN activity modulated by HPA axis sensitivity was observed in the cerebellum, as well as HPA axis modulated downregulation in the occipital pole ($p < .01$, uncorrected). However, these clusters did not survive correction for multiple comparisons.

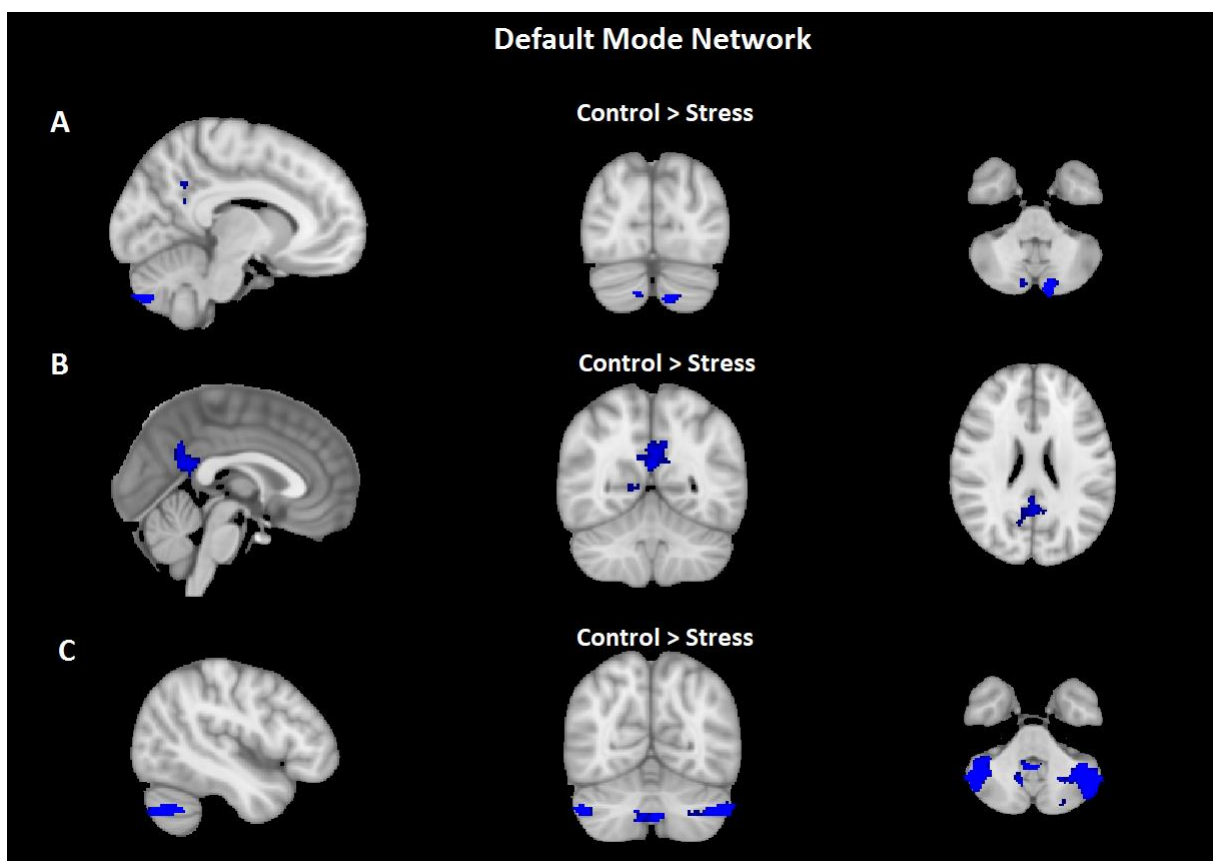


Figure 5: Stress-induced decreased connectivity between the dorsal Default Mode Network and the cerebellum (A), as well as with the posterior cingulate cortex (B). Cerebellar connectivity was also decreased with the ventral Default Mode Network (C).

Discussion

The current study investigated the differences in resting-state connectivity of three major large-scale networks (SN, DMN, ECN) under acute stress, and how these might be modulated by HPA-axis sensitivity to stress. The observed changes in functional connectivity across the networks were not modulated by individual HPA-axis sensitivity to the stress induction procedure. This suggests that cortisol may not play a major role in downregulating ECN and DMN connectivity in the acute stress response. However, it may be that other factors play a role in this observation. Firstly, the population sample in the current study contained female participants that were either using hormonal contraceptives or freecycling. Hormonal contraceptive use has a blunting effect on the cortisol response to stressors (Nielsen et al., 2012), therefore we controlled for hormonal contraceptive use in testing the (peak) cortisol difference between the control and stress session, which showed a significant difference. The HPA-index utilized in this study has previously been successfully used to map individual stress sensitivity and predict the neural response to stress (Henckens et al., 2016). However, that population consisted of only males while the current study population combines males and females that are either on hormonal contraceptives or free-cycling. This measure might therefore not translate to this wider study population without taking hormonal cycles or contraceptive use into account.

Evidence also suggests that hormonal contraceptive use might affect neural functioning and resting-state connectivity in the DMN and ECN (Peterson, Kilpatrick, Goharзад, & Cahill., 2013). We did not control for hormonal contraceptive use in analyzing the functional data and therefore cannot exclude any effects of hormonal contraceptive use on HPA-axis modulation of functional connectivity, as well as cortisol-independent changes in functional connectivity dynamics across these networks. Unfortunately, group sizes of the current study are insufficient to test for functional differences between males, free cycling females, and hormonal contraceptive taking females. Additionally, the timing of saliva sample acquisition may not have been optimal in the current study design. Saliva samples for peak cortisol levels were collected an average of 37 minutes after stress induction. It is possible that this sample was taken after the actual peak levels of circulating cortisol, as is reached closer to 20-30 minutes after stress (Kirschbaum et al., 1992; Becker & Rohleder, 2019). As the cortisol response varies in time between individuals (Kudielka, Hellhammer, & Wüst, 2009), it might be possible that the calculated HPA-axis sensitivity is not an optimal

reflection of the real magnitude of individual cortisol responses. Alternative measures of individual HPA-axis sensitivity include the Cortisol Awakening Response (Fries, Dettenborn, & Kirschbaum., 2008) and Dexamethasone suppression test (Findling, Raff, & Aron, 2004). However, these measures are not specific to a stressor induced HPA-axis response.

In line with expectations, stress-induced decreased functional connectivity was found within the dorsal DMN, specifically in the posterior cingulate cortex. Decreased connectivity was also observed between the DMN and the cerebellum. Contrary to our hypotheses, no changes in functional connectivity were observed in the SN while the left and right ECN showed decreased functional connectivity with the ipsilateral cerebellum. The right ECN also showed increased functional connectivity with a small cluster in the contralateral cerebellum. Interestingly, the observed changes in these networks were not modulated by individual cortisol responsiveness.

These results suggest that both the DMN and ECN are downregulated in response to acute stress. Our finding of decreased functional connectivity within the DMN fits with a previous report that showed similar findings (Zhang et al., 2019). This within-network decrease was observed in the posterior cingulate cortex/precuneus (PCC/Pcu), which is consistently reported as a core component of the DMN (van Oort et al., 2017). The PCC/Pcu has a heterogeneous set of functions but its role in regulating the focus of attention suggests that downregulation of this area in response to acute stress allows for more global scanning of the environment and could account for the experienced difficulties in focusing attention under stress (Leech & Sharp, 2014; Arnsten, 2009). The PCC is also functionally related to the retrieval of episodic memory, which has also been found to be impaired under acute stress (Maddock, Garrot, & Buonocore, 2001; Gagnon & Wagner, 2016).

An interesting and novel finding of this study is the widespread connectivity changes induced by stress with the cerebellum. Although the functional role of the cerebellum in motor control and learning has been widely established, focus towards its role in cognitive-affective domains has been increasing substantially (Stoodley & Schmahmann, 2010; Strata, 2015). The ICN network templates derived in the current study included cerebellar contributions in all networks except for the ventral DMN. The distinct contributions of cerebellar regions in

our network templates fit closely to earlier reports that identified cerebellar subregion contribution to multiple large-scale networks including the SN, DMN, and ECN (Habar et al., 2009; Castellazzi et al., 2018). Specifically, Lobule VI and crus I were identified as part of the SN, lobule IX as part of the DMN, and crus I-II as part of the ECN with a specific contribution of the right lobule IX to the left ECN. Another study reported the contribution of crus I as part of the DMN as well (Krienen & Buckner, 2009). Our SN group template showed a similar cerebellar contribution. The derived DMN templates did contain lobule IX and crus I with the addition of contributions of crus II and the left lobule VI. The identified ECN network confirmed crus I-II involvement.

Stress-induced functional connectivity decreased between both DMN and ECN with distinct cerebellar regions. For the ventral DMN, these included the bilateral lobule IX (DMN related) and bilateral crus I (SN, DMN, and ECN related) and for the dorsal DMN, this included the bilateral crus II (ECN related). These reduced connectivity patterns with lobule IX and crus I might, therefore, constitute *within-network changes*; as well as *between-network* dynamics via the involvement of crus I in all three networks of interest. Previous work using Dynamic Causal Modeling has shown that the SN orchestrates switching from the DMN—when no active task is present—to the ECN, which is activated upon task execution (Goulden et al., 2014). Therefore, it might be possible that such *between-network* modulation occurs via a common anatomical node, of which we identified crus I as one such candidate region.

The functional role of lobule IX is poorly understood (Habas et al., 2009). However, a recent study has identified this region as part of the dorsal attention network (Ramanoel, York, & Christophe, 2018) and has been shown to have a role in past and future elaboration in conjunction with the PCC/Pcu (Addis, Wong, & Schacter, 2007), and our results show this to have reduced connectivity after stress-induction as well. It might therefore be the case that stress-induced reduction in functional connectivity in these areas contributes to the externalization of attention after acute stress induction.

Crus I is functionally related to executive functions associated with the ECN. These include deductive reasoning (Monti, Osherson, Martinez, & Parsons, 2007) as well as verbal working memory (Chen & Desmond, 2005). It is also related to cognitive functions more associated to

the SN such as emotion processing (Stoodley & Schmahmann, 2009). The functional role of crus I in the DMN is unclear but its role in the ventral attention network and SN suggests it might play a role in types of attention switching in which SN-DMN interactions play a crucial role (Castellazzi et al., 2018; Seeley et al., 2007). Therefore, the reduced connectivity between DMN and crus I might constitute a prominent role in stress-induced attention switching, while reduced crus I connectivity with the ECN—on the other hand—relating to the stress-induced impairment of executive functions. Diminished functional connectivity between the ECN and crus II was furthermore observed. Since crus II is functionally related to verbal fluency (Stoodley, Valera, & Schmahmann, 2012), our finding might be explained through reduced top-down control of language processes; since stress has been shown to impair certain language processes such as word generation. That said, the literature on this subject exhibits mixed findings (Buchanan, Laures-Gore, & Duff, 2014; Nair et al., 2019).

The left and right constituent ECN networks exhibited reduced functional connectivity with the ipsilateral crus I-II of the cerebellum. Interestingly, the ICN network templates contained their contralateral counterparts, which suggests that this might constitute diminished *within-network* synchronization between the counterparts of the ECN in response to acute stress. Cerebellar decoupling within the ECN has been observed to occur in multiple stress-related disorders that include impairments in executive functions in their symptomology; including bipolar and major depressive disorder (Luo et al., 2018; Liu et al., 2012). However, a functional decoupling between the *left* and *right* counterparts of the ECN has not been previously reported in response to acute stress.

Surprisingly, no increased SN connectivity after stress-induction was observed despite previous resting-state functional connectivity studies finding consistent upregulated SN connectivity in response to acute stress (Zhang et al., 2019; van Oort et al., 2017). In consideration of this discrepancy from previous findings, it is worth noting that a large subset of studies that observed increases in SN connectivity used seed-based connectivity analysis with the seed placed in the amygdala (van Oort et al., 2017), while the ICA derived network group templates produced in Zhang et al. contained the amygdala as well. Since the SN ICN template of the current study did not contain the amygdala, it is plausible that we failed to observe SN upregulation due to the absence of this core region. Similarly, the

timing of our measures could have played a role in this discrepancy as well. Stress induced SN upregulation appears to be mechanistically related to norepinephrine, rather than cortisol (Hermans et al., 2011). This could imply that the relatively shorter onset time of action of norepinephrine happened to enhance SN resting-state functional connectivity prior to measurement, and accordingly dissipated at the time of measurement. Salivary alpha-amylase can be used as a biomarker for norepinephrine levels (Thoma, Kirschbaum, Wolf, & Rohleder, 2012) and might therefore show a modulatory role of SN FC where cortisol does not.

This study is the first study that contrasted stress-induced FC changes with a non-stressful separate control session. Although FC strength and network topography can be reliably extracted between subjects and groups (Van Dijk et al., 2010; Fox et al., 2005), one limitation to this approach is the relatively poor within-subject test-retest reliability of ICA derived resting-state networks (Poppe et al., 2013). Run structure was optimized for this protocol including subject task (i.e. open eyes fixation), acquisition length, and temporal and spatial resolution (Van Dijk et al., 2010). Therefore, there is minimal room left for optimization of these parameters and careful consideration of this limitation should be considered in future studies assessing individual differences in large-scale network functional connectivity with repeated measures.

The current study demonstrates downregulated DMN and ECN functional connectivity throughout the cerebellum, independently of the cortisol response, after acute stress under rest conditions. Future research would be well placed to include cerebellar regions in resting-state network investigations. The findings in the current study could potentially aid in subsequent investigations into the precise functional role of cerebellar regions in cognition, and how these are in turn affected by stress and stress-related psychopathology.

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References

- Addis, D. R., Wong, A. T., & Schacter, D. L. (2007). Remembering the past and imagining the future: Common and distinct neural substrates during event construction and elaboration. *Neuropsychologia*, 45(7), 1363–1377. <https://doi.org/10.1016/j.neuropsychologia.2006.10.016>
- Arnsten, A. F. T. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. *Nature Reviews Neuroscience*, 10(6), 410–422. <https://doi.org/10.1038/nrn2648>
- Aston-Jones, G., & Cohen, J. D. (2005). AN INTEGRATIVE THEORY OF LOCUS COERULEUS-NOREPINEPHRINE FUNCTION: Adaptive Gain and Optimal Performance. *Annual Review of Neuroscience*, 28(1), 403–450. <https://doi.org/10.1146/annurev.neuro.28.061604.135709>
- Barsegyan, A., Mackenzie, S. M., Kurose, B. D., McGaugh, J. L., & Roozendaal, B. (2010). Glucocorticoids in the prefrontal cortex enhance memory consolidation and impair working memory by a common neural mechanism. *Proceedings of the National Academy of Sciences*, 107(38), 16655–16660. <https://doi.org/10.1073/pnas.1011975107>
- Becker, L., & Rohleder, N. (2019). Time course of the physiological stress response to an acute stressor and its associations with the primacy and recency effect of the serial position curve. *PLOS ONE*, 14(5), e0213883. <https://doi.org/10.1371/journal.pone.0213883>

- Beckmann, C., Mackay, C., Filippini, N., & Smith, S. (2009). Group comparison of resting-state FMRI data using multi-subject ICA and dual regression. *NeuroImage*, 47, S148. [https://doi.org/10.1016/S1053-8119\(09\)71511-3](https://doi.org/10.1016/S1053-8119(09)71511-3)
- Beckmann, C.F., & Smith, S. M. (2005). Tensorial extensions of independent component analysis for multisubject FMRI analysis. *NeuroImage*, 25(1), 294–311. <https://doi.org/10.1016/j.neuroimage.2004.10.043>
- Beckmann, Christian F, DeLuca, M., Devlin, J. T., & Smith, S. M. (2005). Investigations into resting-state connectivity using independent component analysis. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 360(1457), 1001–1013. <https://doi.org/10.1098/rstb.2005.1634>
- Birn, R. M., Molloy, E. K., Patriat, R., Parker, T., Meier, T. B., Kirk, G. R., Nair, V. A., Meyerand, M. E., & Prabhakaran, V. (2013). The effect of scan length on the reliability of resting-state fMRI connectivity estimates. *NeuroImage*, 83, 550–558. <https://doi.org/10.1016/j.neuroimage.2013.05.099>
- Birnbaum, S., Gobeske, K. T., Auerbach, J., Taylor, J. R., & Arnsten, A. F. T. (1999). A Role for Norepinephrine in Stress-Induced Cognitive Deficits: α -1-Adrenoceptor Mediation in the Prefrontal Cortex. *BIOL Psychiatry*, 46, 1266-1274.
- Bressler, S. L., & Menon, V. (2010). Large-scale brain networks in cognition: Emerging methods and principles. *Trends in Cognitive Sciences*, 14(6), 277–290. <https://doi.org/10.1016/j.tics.2010.04.004>
- Cannon, W. B. (1915). *Bodily changes in pain, hunger, fear and rage: An account of recent researches into the function of emotional excitement*. D Appleton & Company. <https://doi.org/10.1037/10013-000>
- Cannon, W. B. (1929). ORGANIZATION FOR PHYSIOLOGICAL HOMEOSTASIS. *Physiological Reviews*, 9(3), 399–431. <https://doi.org/10.1152/physrev.1929.9.3.399>
- Castellazzi, G., Bruno, S. D., Toosy, A. T., Casiraghi, L., Palesi, F., Savini, G., D'Angelo, E., & Wheeler-Kingshott, C. A. M. G. (2018). Prominent Changes in Cerebro-Cerebellar Functional Connectivity

During Continuous Cognitive Processing. *Frontiers in Cellular Neuroscience*, 12, 331.

<https://doi.org/10.3389/fncel.2018.00331>

Chen, S. H. A., & Desmond, J. E. (2005). Cerebrocerebellar networks during articulatory rehearsal and verbal working memory tasks. *NeuroImage*, 24(2), 332–338.

<https://doi.org/10.1016/j.neuroimage.2004.08.032>

Chiba, T., Kanazawa, T., Koizumi, A., Ide, K., Taschereau-Dumouchel, V., Boku, S., Hishimoto, A., Shirakawa, M., Sora, I., Lau, H., Yoneda, H., & Kawato, M. (2019). Current Status of Neurofeedback for Post-traumatic Stress Disorder: A Systematic Review and the Possibility of Decoded Neurofeedback.

Frontiers in Human Neuroscience, 13, 233. <https://doi.org/10.3389/fnhum.2019.00233>

Clemens, B., Wagels, L., Bauchmüller, M., Bergs, R., Habel, U., & Kohn, N. (2017). Alerted default mode: Functional connectivity changes in the aftermath of social stress. *Scientific Reports*, 7(1), 40180.

<https://doi.org/10.1038/srep40180>

de Kloet, E. R., Joëls, M., & Holsboer, F. (2005). Stress and the brain: From adaptation to disease. *Nature Reviews Neuroscience*, 6(6), 463–475. <https://doi.org/10.1038/nrn1683>

Dice, L. R. (1945). Measures of the Amount of Ecologic Association Between Species. *Ecology*, 26(3), 297–302. <https://doi.org/10.2307/1932409>

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., & Raichle, M. E. (n.d.). *The human brain is intrinsically organized into dynamic, anticorrelated functional networks*. 6.

Gagnon, S. A., & Wagner, A. D. (2016). Acute stress and episodic memory retrieval: Neurobiological mechanisms and behavioral consequences: Acute stress and episodic memory retrieval. *Annals of the New York Academy of Sciences*, 1369(1), 55–75. <https://doi.org/10.1111/nyas.12996>

Guo, W., Liu, F., Liu, J., Yu, M., Zhang, Z., Liu, G., Xiao, C., & Zhao, J. (2015). Increased Cerebellar-Default-Mode-Network Connectivity in Drug-Naive Major Depressive Disorder at Rest: *Medicine*, 94(9), e560.

<https://doi.org/10.1097/MD.0000000000000560>

- Habas, C., Kamdar, N., Nguyen, D., Prater, K., Beckmann, C. F., Menon, V., & Greicius, M. D. (2009). Distinct Cerebellar Contributions to Intrinsic Connectivity Networks. *Journal of Neuroscience*, *29*(26), 8586–8594. <https://doi.org/10.1523/JNEUROSCI.1868-09.2009>
- Hermans, E. J., Henckens, M. J. A. G., Joëls, M., & Fernández, G. (2014). Dynamic adaptation of large-scale brain networks in response to acute stressors. *Trends in Neurosciences*, *37*(6), 304–314. <https://doi.org/10.1016/j.tins.2014.03.006>
- Joëls, M., Fernandez, G., & Roozendaal, B. (2011). Stress and emotional memory: A matter of timing. *Trends in Cognitive Sciences*, *15*(6), 280–288. <https://doi.org/10.1016/j.tics.2011.04.004>
- Kirschbaum, C., Bartussek, D., & Strasburger, C. J. (1992). Cortisol responses to psychological stress and correlations with personality traits. *Personality and Individual Differences*, *13*(12), 1353–1357. [https://doi.org/10.1016/0191-8869\(92\)90181-N](https://doi.org/10.1016/0191-8869(92)90181-N)
- Kral, T. R. A., Schuyler, B. S., Mumford, J. A., Rosenkranz, M. A., Lutz, A., & Davidson, R. J. (2018). Impact of short- and long-term mindfulness meditation training on amygdala reactivity to emotional stimuli. *NeuroImage*, *181*, 301–313. <https://doi.org/10.1016/j.neuroimage.2018.07.013>
- Krienen, F. M., & Buckner, R. L. (2009). Segregated Fronto-Cerebellar Circuits Revealed by Intrinsic Functional Connectivity. *Cerebral Cortex*, *19*(10), 2485–2497. <https://doi.org/10.1093/cercor/bhp135>
- Kudielka, B. M., Hellhammer, D. H., & Wüst, S. (2009). Why do we respond so differently? Reviewing determinants of human salivary cortisol responses to challenge. *Psychoneuroendocrinology*, *34*(1), 2–18. <https://doi.org/10.1016/j.psyneuen.2008.10.004>
- Leech, R., & Sharp, D. J. (2014). The role of the posterior cingulate cortex in cognition and disease. *Brain*, *137*(1), 12–32. <https://doi.org/10.1093/brain/awt162>
- Maddock, R. J., Garrett, A. S., & Buonocore, M. H. (2001). Remembering familiar people: The posterior cingulate cortex and autobiographical memory retrieval. *Neuroscience*, *104*(3), 667–676. [https://doi.org/10.1016/S0306-4522\(01\)00108-7](https://doi.org/10.1016/S0306-4522(01)00108-7)

- Magezi, D. A. (2015). Linear mixed-effects models for within-participant psychology experiments: An introductory tutorial and free, graphical user interface (LMMgui). *Frontiers in Psychology*, 6, 2. <https://doi.org/10.3389/fpsyg.2015.00002>
- Mason, J. W. (1968). A Review of Psychoendocrine Research on the Sympathetic-Adrenal Medullary System: *Psychosomatic Medicine*, 30(5), 631–653. <https://doi.org/10.1097/00006842-196809000-00022>
- McReynolds, J. R., Donowho, K., Abdi, A., McGaugh, J. L., Roozendaal, B., & McIntyre, C. K. (2010). Memory-enhancing corticosterone treatment increases amygdala norepinephrine and Arc protein expression in hippocampal synaptic fractions. *Neurobiology of Learning and Memory*, 93(3), 312–321. <https://doi.org/10.1016/j.nlm.2009.11.005>
- Meijer, O. C., Buurstede, J. C., & Schaaf, M. J. M. (2019). Corticosteroid Receptors in the Brain: Transcriptional Mechanisms for Specificity and Context-Dependent Effects. *Cellular and Molecular Neurobiology*, 39(4), 539–549. <https://doi.org/10.1007/s10571-018-0625-2>
- Monti, M. M., Osherson, D. N., Martinez, M. J., & Parsons, L. M. (2007). Functional neuroanatomy of deductive inference: A language-independent distributed network. *NeuroImage*, 37(3), 1005–1016. <https://doi.org/10.1016/j.neuroimage.2007.04.069>
- Nair, N., Hegarty, J. P., Ferguson, B. J., Hooshmand, S. J., Hecht, P. M., Tilley, M., Christ, S. E., & Beversdorf, D. Q. (2019). Effects of stress on functional connectivity during verbal processing. *Brain Imaging and Behavior*. <https://doi.org/10.1007/s11682-019-00221-5>
- Nickerson, L. D., Smith, S. M., Öngür, D., & Beckmann, C. F. (2017). Using Dual Regression to Investigate Network Shape and Amplitude in Functional Connectivity Analyses. *Frontiers in Neuroscience*, 11. <https://doi.org/10.3389/fnins.2017.00115>

- Nielsen, S. E., Segal, S. K., Worden, I. V., Yim, I. S., & Cahill, L. (2013). Hormonal contraception use alters stress responses and emotional memory. *Biological Psychology*, *92*(2), 257–266.
<https://doi.org/10.1016/j.biopsycho.2012.10.007>
- Patel, V., Chisholm, D., Parikh, R., Charlson, F. J., Degenhardt, L., Dua, T., Ferrari, A. J., Hyman, S., Laxminarayan, R., Levin, C., Lund, C., Medina Mora, M. E., Petersen, I., Scott, J., Shidhaye, R., Vijayakumar, L., Thornicroft, G., & Whiteford, H. (2016). Addressing the burden of mental, neurological, and substance use disorders: Key messages from Disease Control Priorities, 3rd edition. *The Lancet*, *387*(10028), 1672–1685. [https://doi.org/10.1016/S0140-6736\(15\)00390-6](https://doi.org/10.1016/S0140-6736(15)00390-6)
- Piazza, J. R., Almeida, D. M., Dmitrieva, N. O., & Klein, L. C. (2010). Frontiers in the Use of Biomarkers of Health in Research on Stress and Aging. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *65B*(5), 513–525. <https://doi.org/10.1093/geronb/gbq049>
- Poser, B. A., Versluis, M. J., Hoogduin, J. M., & Norris, D. G. (2006). BOLD contrast sensitivity enhancement and artifact reduction with multiecho EPI: Parallel-acquired inhomogeneity-desensitized fMRI. *Magnetic Resonance in Medicine*, *55*(6), 1227–1235. <https://doi.org/10.1002/mrm.20900>
- Posse, S. (2012). Multi-echo acquisition. *NeuroImage*, *62*(2), 665–671.
<https://doi.org/10.1016/j.neuroimage.2011.10.057>
- Pruim, R. H. R., Mennes, M., van Rooij, D., Llera, A., Buitelaar, J. K., & Beckmann, C. F. (2015). ICA-AROMA: A robust ICA-based strategy for removing motion artifacts from fMRI data. *NeuroImage*, *112*, 267–277. <https://doi.org/10.1016/j.neuroimage.2015.02.064>
- Rajkowski, J., Kubiak, P., Ivanova, S., & Aston-Jones, G. (1997). State-Related Activity, Reactivity of Locus Ceruleus Neurons in Behaving Monkeys. In *Advances in Pharmacology* (Vol. 42, pp. 740–744). Elsevier. [https://doi.org/10.1016/S1054-3589\(08\)60854-6](https://doi.org/10.1016/S1054-3589(08)60854-6)
- Ramanoel, S., York, E., & Habas, C. (2018). Participation of the caudal cerebellar lobule IX to the dorsal attentional network. *Cerebellum & Ataxias*, *5*(1), 9. <https://doi.org/10.1186/s40673-018-0088-8>

- Roosendaal, B., McEwen, B. S., & Chattarji, S. (2009). Stress, memory and the amygdala. *Nature Reviews Neuroscience*, 10(6), 423–433. <https://doi.org/10.1038/nrn2651>
- Roosendaal, B., Williams, C. L., & McGaugh, J. L. (1999). Glucocorticoid receptor activation in the rat nucleus of the solitary tract facilitates memory consolidation: Involvement of the basolateral amygdala: Glucocorticoid effects on memory in the solitary tract N. *European Journal of Neuroscience*, 11(4), 1317–1323. <https://doi.org/10.1046/j.1460-9568.1999.00537.x>
- Russell, G., & Lightman, S. (2019). The human stress response. *Nature Reviews Endocrinology*, 15(9), 525–534. <https://doi.org/10.1038/s41574-019-0228-0>
- Saal, D., Dong, Y., Bonci, A., & Malenka, R. C. (2003). Drugs of Abuse and Stress Trigger a Common Synaptic Adaptation in Dopamine Neurons. *Neuron*, 37(4), 577–582. [https://doi.org/10.1016/S0896-6273\(03\)00021-7](https://doi.org/10.1016/S0896-6273(03)00021-7)
- Schwabe, L., Joëls, M., Roosendaal, B., Wolf, O. T., & Oitzl, M. S. (2012). Stress effects on memory: An update and integration. *Neuroscience & Biobehavioral Reviews*, 36(7), 1740–1749. <https://doi.org/10.1016/j.neubiorev.2011.07.002>
- Selye, H. (1936). A Syndrome produced by Diverse Nocuous Agents. *Nature*, 138, 32. <https://doi.org/10.1038/138032a0>
- Selye H. (1976) Stress without Distress. In: Serban G. (eds) Psychopathology of Human Adaptation. Springer, Boston, MA. https://doi.org/10.1007/978-1-4684-2238-2_9
- Shirer, W. R., Ryali, S., Rykhlevskaia, E., Menon, V., & Greicius, M. D. (2012). Decoding Subject-Driven Cognitive States with Whole-Brain Connectivity Patterns. *Cerebral Cortex*, 22(1), 158–165. <https://doi.org/10.1093/cercor/bhr099>
- Stoodley, C. J., Valera, E. M., & Schmahmann, J. D. (2012). Functional topography of the cerebellum for motor and cognitive tasks: An fMRI study. *NeuroImage*, 59(2), 1560–1570. <https://doi.org/10.1016/j.neuroimage.2011.08.065>

Strata, P. (2015). The Emotional Cerebellum. *The Cerebellum*, 14(5), 570–577.

<https://doi.org/10.1007/s12311-015-0649-9>

Van Dijk, K. R. A., Hedden, T., Venkataraman, A., Evans, K. C., Lazar, S. W., & Buckner, R. L. (2010). Intrinsic Functional Connectivity As a Tool For Human Connectomics: Theory, Properties, and Optimization.

Journal of Neurophysiology, 103(1), 297–321. <https://doi.org/10.1152/jn.00783.2009>

van Oort, J., Tendolkar, I., Hermans, E. J., Mulders, P. C., Beckmann, C. F., Schene, A. H., Fernández, G., & van Eijndhoven, P. F. (2017). How the brain connects in response to acute stress: A review at the human brain systems level. *Neuroscience & Biobehavioral Reviews*, 83, 281–297.

<https://doi.org/10.1016/j.neubiorev.2017.10.015>

Whitfield-Gabrieli, S., & Ford, J. M. (2012). Default Mode Network Activity and Connectivity in Psychopathology. *Annual Review of Clinical Psychology*, 8(1), 49–76.

<https://doi.org/10.1146/annurev-clinpsy-032511-143049>

Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M., & Nichols, T. E. (2014). Permutation inference for the general linear model. *NeuroImage*, 92, 381–397.

<https://doi.org/10.1016/j.neuroimage.2014.01.060>

Young, C. B., Raz, G., Everaerd, D., Beckmann, C. F., Tendolkar, I., Hendler, T., Fernández, G., & Hermans, E. J. (2017). Dynamic Shifts in Large-Scale Brain Network Balance As a Function of Arousal. *The Journal of Neuroscience*, 37(2), 281–290. <https://doi.org/10.1523/JNEUROSCI.1759-16.2016>

Zou, K. H., Warfield, S. K., Bharatha, A., Tempany, C. M. C., Kaus, M. R., Haker, S. J., Wells, W. M., Jolesz, F. A., & Kikinis, R. (2004). Statistical validation of image segmentation quality based on a spatial overlap index1. *Academic Radiology*, 11(2), 178–189. [https://doi.org/10.1016/S1076-6332\(03\)00671-8](https://doi.org/10.1016/S1076-6332(03)00671-8)

