Stress and Motivation: An fMRI Study on the Effects of Stress on Effort-Based Decision-Making

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Reaching desired goals requires effort. In daily life, we often face important decisions on whether to engage in effortful yet rewarding actions (e.g., studying hard to obtain a university degree or accepting a demanding job with a great salary). These decisions are often made under considerable stress, such as when having financial uncertainty. Previous studies have shown that effort-based decision-making implicates a cortico-subcortical network involving the prefrontal cortex and midbrain catecholamine (noradrenaline and dopamine). Stress is known to affect both prefrontal activity and catecholamine levels. Despite these commonalities, the effect of stress on effort-based decision-making and its neural correlates are surprisingly understudied. In this study, the effects of stress on effort-based decision-making were investigated, focusing on behaviour, neural activity, and noradrenergic release measured by pupil dilation. Using a within-subjects design with acute stress induction, we hypothesized that stress would decrease the willingness to engage in mental effort, and that this would be linked with alterations in prefrontal activity and pupil dilation. Participants performed an effort-based decision-making task in the functional magnetic resonance imaging (fMRI) scanner during a control condition or an experimentally induced acute stress condition. The results showed that stress reduced the willingness to engage in effort. Pupil dilation increased with task difficulty during calculations, but did not change under stress. Unexpectedly, no difference was observed between stress and control at the whole-brain level. An a-priori region-of-interest analysis revealed no significant effect of stress on effort or reward coding in the anterior cingulate cortex (ACC). A significant decrease in effort coding under stress in the dorsolateral prefrontal cortex (DLPFC) was observed. However, this was specific to the high reward condition and for participants who experienced the control session first. Overall, these results suggest that acute stress reduces the willingness to engage in mental effort, with preliminary evidence of alterations in DLPFC.

KEYWORDS stress, effort-based decision-making, DLPFC, MPFC, ACC, motivation, effort, reward

We often face decisions where we have to figure out whether the goals of our actions are worth the effort. For example, think about choosing what kind of dinner to make for yourself. You could choose from a large range of recipes, ranging from easy to hard. Each recipe has an expected reward: the produced meal. When deciding, you make a trade-off between the effort and expected reward of each option, and try to select the optimal action. However, this decision can be influenced by external factors. For example, you might be under stress due to having an important deadline later. This might influence the amount of effort you are willing to expend for making the dinner, and how you perceive the reward of the dinner itself. Therefore, the trade-off between required effort and expected reward – a typical cost-benefit calculation of effort-based decision-making – might be influenced by stress. Research in humans and animals has shown that stress has a substantial impact on several cognitive functions, such as memory, emotion and attention (Schwabe, Joëls, Roozendaal, Wolf, & Oitzl, 2012; Roozendaal, McReynolds, & McGaugh, 2004; Booth & Sharma, 2009), including preliminary evidence that acute stress may alter motivation (Ironside, Kumar, Kang, & Pizzagalli, 2018). In the following subsections, I will be providing a brief over-view of the known dynamics of effort-based decision-making and stress. Moreover, I will elaborate on the relevant neural mechanisms of these processes and explain the known neural activity underlying these processes.

Effort-based decision-making

In effort-based decision-making, the trade-off between effort and reward is studied. Generally, when people face a decision, they avoid exerting effort (Kool, McGuire, Rosen, & Botvinick, 2010). However, they are willing to exert effort if this leads to a reward (Vassena, Deraeve, & Alexander, 2019). It has been shown that increasing reward causes willingness to exert increasing effort (Shenhav et al., 2017). Additionally, rewards might be valued less when more effort is required to obtain them (Apps, Grima, Manohar, & Husain, 2015). Based on this reward value, and the effort required to obtain the reward, an action is selected. Then, the outcome of

the action is used to update the expected effort and reward.

Extensive neuroscientific research has addressed the neural mechanisms of effort-based decision-making, demonstrating the important role of catecholamines – dopamine (DA) released by the Ventral Tegmental Area (VTA) and noradrenaline (NA) released by the Locus Coeruleus (LC). Animal studies have shown that DA depletion led to increased sensitivity to response cost (Salamone, Correa, Farrar, Nunes, & Pardo, 2009), resulting in rats avoiding more effort. Further, increasing DA transmission increased effortful behaviour in rats (Salamone, Correa, Yang, Rotolo, & Presby, 2018), and blocking DA caused effort avoidance (Walton et al., 2009). In a study in monkeys, DA neurons encoded reward expectation and anticipated effort cost (Varazzani, San-Galli, Gilardeau, & Bouret, 2015). DA is relevant in reward prediction error coding as well as reward valuation (Schultz, 2016). Research shows that DA depletion can lead to reduced effortful behaviour (Salamone, Cousins, & Bucher, 1994) and that DA is needed for motivation (Berridge, 2012). Therefore, DA can influence effort-based decision-making, by regulating both the effort and reward signals. Dopaminergic input to dorsal Anterior Cingulate Cortex (dACC), part of the medial prefrontal cortex (MPFC), is associated with prediction error and reward expectation (Schultz, Dayan, & Montague, 1997; Pan, Schmidt, Wickens, & Hyland, 2005). It was also reported that VTA-mediated DA release has a role in cost encoding (Orsini, Hernandez, Bizon, & Setlow, 2018), and thus influences effort-based decision-making. Given the aforementioned role of DA in effort-based decision-making, and given that the VTA produces DA, a role for the VTA seems prominent in decision-making.

Complementary to DA, NA has also been implicated in effort-based decision-making (Varazzani et al. 2015). LC activity correlated with effort coding and changes in reward (Bouret & Richmond, 2009; Varazzani et al., 2015). Further, NA levels have been connected to performance in an optimization task through modulation of the learning parameter (Ironside et al., 2018). A correlation between pupil size and effort coding has also been found (Varazzani et al., 2015). Noradren-ergic input to dACC is also thought to reflect

environmental volatility (Behrens, Woolrich, Walton, & Rushworth, 2007; Silvetti, Seurinck, van Bochove, & Verguts, 2013a). Taken together, these findings suggest that LC-NA can influence effortful decision-making. Additionally, a role for the Striatum, one of the primary targets of midbrain dopaminergic projections, has been reported (Orsini et al., 2018).

In humans, previous research on neural correlates of effort-based decision-making indicated that the MPFC and dorsolateral prefrontal cortex (DLPFC) show effort-related activity (Vassena, Deraeve, & Alexander, 2017). Besides effort, the DLPFC shows reward-related activity (Asci, Braem, Park, Boehler, & Krebs, 2019). Furthermore, the dACC has a role in effort coding, even independently of reward given (Porter, Hillman, & Bilkey, 2019), and plays a role in optimal action selection (Silvetti, Vassena, Abrahamse, & Verguts, 2018). ACC and striatum activity are also reported when anticipating reward and effort (Vassena et al., 2014); a study in rats found that a lesion in the ACC caused rats to select lower effort choices more often (Walton et al., 2009). Thus, given that effort-based decision-making combines reward and effort, a model that captures effort-based decision-making should incorporate both reward and effort. This line of work led to developing the reinforcement meta-learner model (RML), taking both reward and effort into account (Silvetti et al., 2018).

This model consists of two separate subparts. First, there is an action selection mechanism. This mechanism contains the network of MPFC, DLPFC and dACC, which are all involved in effort or reward-related activity. Second, there is a meta-learning mechanism. This mechanism consists of the dACC and the brainstem nuclei releasing catecholamines; the VTA releasing DA, and the LC releasing NA (Silvetti et al., 2018). The RML builds on earlier models, implementing the idea that information about reward, prediction error and volatility is fundamental to determine which are the best actions to perform (Behrens et al., 2007; Silvetti, Seurinck, & Verguts, 2013b; Alexander & Brown, 2011). The critical insight of the RML and the core of the meta-learning aspect is that the dACC can in turn top-down influence catecholamine release in VTA and LC, and

therefore adapt its own parameters (Silvetti et al., 2018). This mechanism is particularly important when higher NA levels are needed to invigorate a more effortful action, or when higher DA levels are needed to pursue long-term rewards that are not available yet. In these situations, dACC is able to upregulate NA or DA release to support flexible and adaptive behaviour (Silvetti et al., 2018). This model provides a promising neuro-computational framework to understand the role of prefrontal and catecholaminergic dynamics during decision-making.

Mechanisms of stress

Stressors are defined as perceived threats to homeostasis and well-being (Herman et al., 2016). Exposure to stressors triggers a series of neurophysiological events known as the stress response which allow prompt behavioural responses in challenging situations. This stress reaction can be adaptive or maladaptive. In this case, it can lead to the development of stress-related disorders, e.g. Post-Traumatic Stress Disorder. The stress response originates from two different systems: a slow system and a fast system (Hermans, Henckens, Joëls, & Fernández, 2014).

The fast stress response occurs almost instantly, and lasts for 30-60 minutes (Joëls & Baram, 2009). It is characterized by a substantial increase in catecholamine levels. During this response, the LC is activated (Valentio & Bockstaele, 2008) and NA is released. DA levels also increase, especially in the MPFC (Hermans et al., 2014). Furthermore, a shift in network balance can be observed after stress. In the early stress response, an increase of neural activity in the salience network (SN) is observed. The SN includes a number of cortical and subcortical regions, including dACC and insula, that are generally more active when we experience salient events (Seeley et al., 2007; Hermans et al., 2011). At the same time, a decrease in neural activity is observed in the executive control network (ECN). The ECN includes regions that are generally more active when we engage in mentally demanding tasks which require cognitive control. This network includes dorsolateral and dorsomedial parts of the PFC (Seeley et al., 2007; Hermans et al., 2011;

Hermans et al., 2014).

Interestingly, this shift from ECN to SN reverses after the early stress response is over (Hermans et al., 2014; see Fig. 1 for a summary). This phenomenon has been linked to the interplay with the glucocorticoid system. After the initial fast response, a slower process is initiated, involving the hypothalamic-pituitary-adrenal (HPA) axis. In this response, corticosteroid levels increase. These corticosteroids, which are cortisol and corticosterone, have an effect on two different time scales. They have a direct, non-genomic effect, reaching their peak after the catecholaminergic effect, and a slower, genomic effect (Hermans et al., 2014; Joëls, Sarabdjitsingh, & Karst, 2012). This non-genomic effect causes an increase in NA activity, and enhances the stress effects on DA (Hermans et al., 2014). Furthermore, these effects were found to impair working memory

in rats (Roozendaal et al., 2004). However, after this initial impairment, long-term effects of corticosteroids were found to increase PFC function and improve working memory in rats (Yuen et al., 2009).

Stress effects on decision-making

The neural basis of decision-making and the effect of stress on behaviour have largely been studied by independent research lines. Yet, these lines of work clearly suggest that there is overlap in the neural circuits active during both stress and decision-making (Silvetti et al., 2018; Valentino & Bockstaele, 2008; Gathmann et al., 2014), especially in the dACC, DLPFC, and MPFC. It was also found that these catecholamines are involved in both stress and effort-based decision-making (Ironside et al., 2018); stress increases DA and NA production
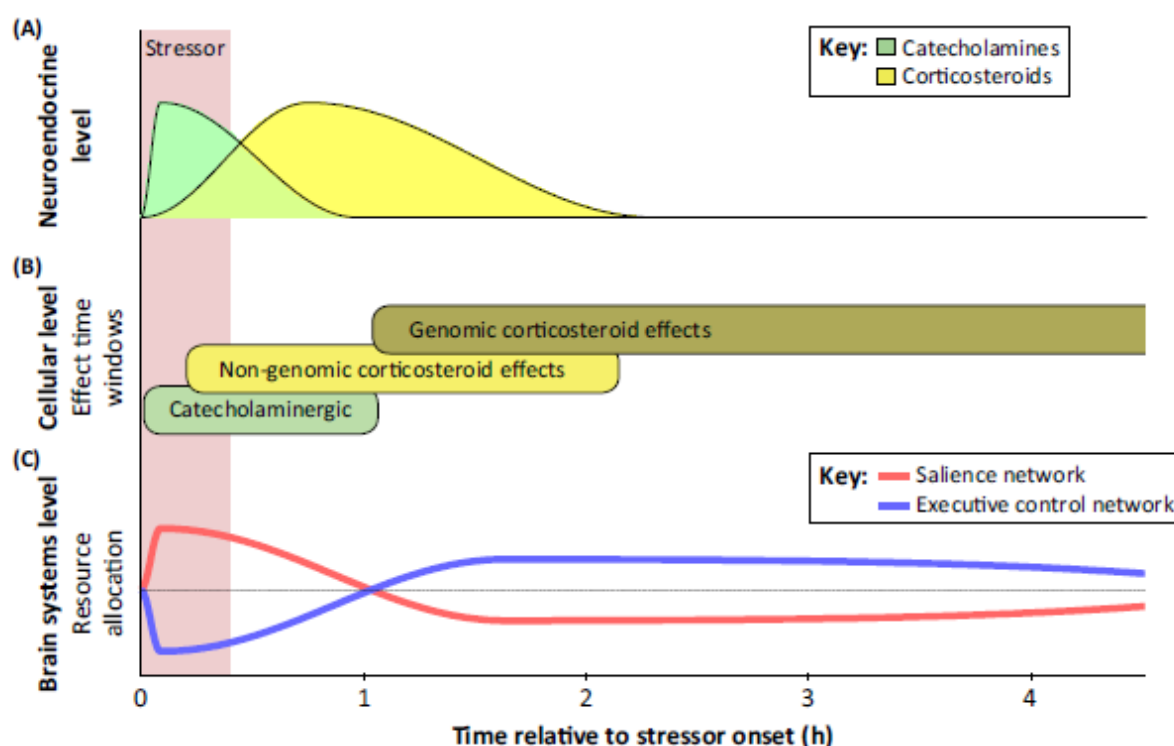

Figure 1. The early and late stress response. A. The stress response on the neuroendocrine level. At stress onset, an increase in catecholamines can be observed, which gradually decreases, and stops 30 - 60 minutes after stress onset. Meanwhile, an increase in corticosteroid levels be observed. B. The effects on the cellular level. In the early stress response, a catecholaminergic effect can be observed, until 30 - 60 minutes after stress onset. Afterwards, the non-genomic effects of corticosteroids start. Finally, the genomic effects of corticosteroids can be seen. C. The effect of stress on the brain systems level. We can see that directly after stress, there is a boost of the salience network (SN), while the resources allocated towards the executive control network (ECN) decrease. After the initial stress response, this effect switches around, causing an increase in resource allocation in the ECN and a decrease in resource allocation in the SN. Figure taken from Hermans et al. (2014).

which both have an influence on decision-making. Interestingly, effects of stress on some types of decision-making were found. For example, stress tends to drive humans towards habitual decisions, and away from goal-directed behaviour (Schwabe & Wolf, 2009). Additionally, a review by Starcke & Brand (2012) suggests that acute stress has a task-specific effect on reward perception and impairs decision strategy selection by stopping the search for alternatives early. Furthermore, acute stress increases risk-seeking behaviour in ambiguous tasks. More specifically, stressed participants are drawn to riskier high-reward choices even when such choices are not optimal (Starcke & Brand, 2016).

Moreover, it has been shown that stress influences motivation via the VTA in rats (Hollon, Burgeno, & Phillips, 2015; Tye et al., 2012) by causing insensitivity to reward and an increase in avoiding effort. Additionally, chronic stress was found to increase anhedonia (Tye et al., 2012; Willner, Towell, Sampson, Sophokleous, & Muscat, 1987). Finally, loss of motivation is one of the hallmarks of several stress-related disorders, including burnout and PTSD (Husain & Roiser, 2018; Lyndon et al., 2017). Overall, these findings indicate that stress might influence reward perception, and hence potentially impair the willingness to exert effort for reward.

Aim of this study

Although several research lines state that stress may affect the willingness to engage in effort and the neural systems implicated in effort-based decision-making, these mechanisms remain poorly understood. Thus, the aim of this study was to further elucidate the effect of stress on effort-based decision-making in healthy humans. It was hypothesised that acute stress influences effort-based decision-making, particularly by decreasing the willingness to engage in mental effort. This reduction may be driven by either an increase in the avoidance of effort, or a decrease in reward sensitivity. Furthermore, it was hypothesised that this effect of stress is linked to alterations in prefrontal activity, especially in the MPFC and DLPFC. Furthermore, as studies in

humans have measured pupil dilation as a proxy for noradrenergic release (Gilzenrat, Nieuwenhuis, Jepma, & Cohen, 2010; Silvetti et al. ,2013b) and pupil dilation is shown to track the optimization of decision-making in volatile environments (Silvetti et al., 2013b), pupil changes were hypothesised to track effort and the impact of stress as a proxy for putatively increased noradrenergic release.

To test these hypotheses, participants performed an effort-based decision-making task in the magnetic resonance imaging (MRI) scanner; once during a control condition, and once while under acute stress. Acute stress was experimentally induced using the socially evaluated cold pressor task (SECPT) (Schwabe, Haddad, & Schachinger, 2008). During the task, participants were offered the choice to engage in calculations of varying difficulty levels for either small or large rewards. The participants did not perform these calculations until after the MRI scan. Additionally, participants performed calculations in the scanner. These are independent of their choices, in order to dissociate decision-related from performance-related activity. This was done in order to measure their accuracy and the stress effects on working memory. Neural activity was examined at the whole-brain level. Furthermore, two different region-of-interest (ROI) analyses were conducted. One was performed based on an a-priori region-of-interest of the MPFC based on previous literature on effort-based decision-making, and another one using prefrontal regions and the insula (as part of the SN, to do a preliminary analysis of the effect of stress on a network level) based on activity variation with effort recorded during the calculation task.

The results of this study could help clarify the interactions between stress and effort-based decision-making. Specifically, knowledge on how stress influences effort-based decision-making might help in alleviating problems found in patients with stress-related disorders in which motivation is changed, such as burnout and PTSD. Knowledge on the neural mechanisms of the stress effect during motivation might open up another way to improve treatments for these patients. Finally, investigating how stress and effort influence pupil size, as a proxy for noradrenergic release, could provide insights

into the way stress and effort interact with noradrenaline.

Methods

Participants

According to a power analysis performed prior to starting the study, the planned sample size was 35 participants. However, due to the Covid-19 pandemic lockdown, data collection was suspended. Hence, this thesis will only include preliminary analysis on the data from the participants gathered up until the lockdown came into effect. A within-subjects crossover study was performed with 26 participants (age 18-40, mean age 24.5, all right handed, 13 female). Participants were recruited through the SONA recruitment system of the Radboud University, as well as through social media and advertisement. Each participant signed an informed consent form before participating in the study. The study was conducted under the local ethical committee approval (CMO2014/288) and approved by the Donders Centre for Cognitive Neuroimaging. Each participant filled in a safety form before entering the MRI, to exclude participants with metal implants or medical conditions incompatible with entering the scanner. We excluded participants if they were colourblind or had a history of psychiatric disorders or brain surgery. Females were excluded if they used hormonal contraceptives, as this was found to influence stress responsiveness (Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999), and only included if they were in the luteal phase of their cycle during the sessions when they performed the task. Each participant received monetary compensation of 64 euros for their participation, with an additional monetary bonus between 0 and 20 euros depending on their performance. Of these 26 participants, the MRI data from two participants could not be analysed correctly due to a realignment problem for these participants. Additionally, one participant was excluded from the analysis, after reporting that they did not understand the task correctly during their final session.

Design

In this experiment, each participant performed three sessions: one training session, one stress session and one control session. The first session was always the training session. The order of the control and stress session (2nd or 3rd) was counterbalanced across participants.

During the first session, the participants started by filling in the questionnaires (for more detailed information about the questionnaires, see the questionnaire section below), and subsequently completed a training task which included calculations of similar difficulty as the calculations to be
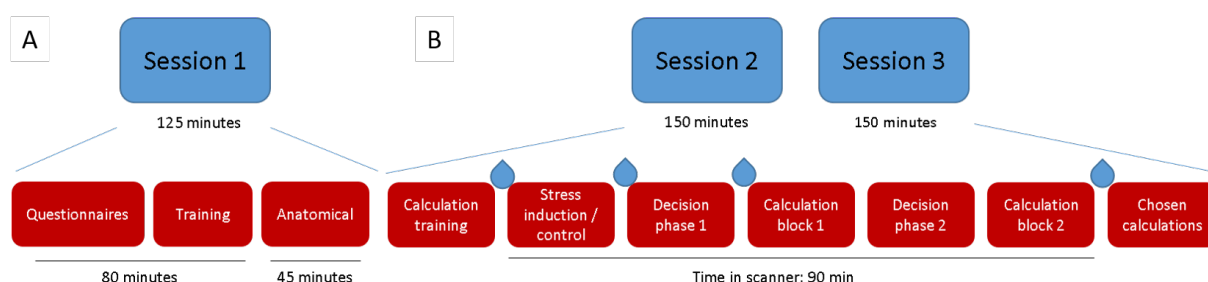

Figure 2. The layout of the different sessions. A. The lay-out of session one. This session started with questionnaires and training calculations. Then, there was a short anatomical scan of 45 minutes. B. The lay-out of sessions two and three. These sessions started with a short calculation training, taking 30 minutes. Then, the participant was set up in the scanner. Next the stress procedure (in the stress session) or control procedure (in the control session) was conducted. After this, four task blocks were performed. Finally, the participant performed the chosen calculations outside of the scanner. During these sessions, saliva was measured at four time points, shown as drops in the figure. The first sample was acquired before the stress or control procedure (t = 0), the second after the stress or control procedure (t = 15). The third sample was acquired after the first decision phase (t = 30). The final sample was acquired at the end of the final task block (t = 75).

performed in subsequent phases. The goal of this task was to let participants practice calculations to avoid training effects later on. Finally, the participants underwent three anatomical MRI scans. See Figure 2A for an overview of the first session.

During the stress session, the participants started with a short calculation training in order to minimize the training effect during the experiment. The participants were set up in the scanner and acute stress was induced using the SECPT (detailed in the stress and control procedure section below). Afterwards, the participants performed the experimental tasks in the scanner. These consisted of two tasks, a decision-making task and a calculation task. Each task consisted of two blocks. During the procedure, saliva samples were collected to obtain cortisol measures as an indication of stress levels (see the saliva sampling section below for details). When the participants finished these tasks, they performed a final task outside the scanner and received a reward. During this session, the participants filled in an adapted version of the short Profile of Mood States questionnaire (POMS) (Shacham, 1983) three times in order to record subjective experience of stress and its effects on mood and energy levels. This happened once before the stress induction, once after the stress induction, and once after coming out of the scanner. See Figure 2B for an overview of the stress session.

During the control session, the participants underwent the same procedure as during the stress session, but with one difference. Instead of the stress induction using the SECPT, a control procedure was implemented. See Figure 2B for an overview.

Session scheduling

In order to minimize stress effects due to entering the MRI scanner or participating in a study, the scheduling of the sessions followed some criteria. We tried to minimize the unintended stress experienced by the participants when entering the MRI scanner by scheduling the second session to take place at most 10 days after the first session. Furthermore, the third session was scheduled to take place between 6 and 10 days after the second session. Both the second and the third session were required to take place at

the same time of the day, and were scheduled to start between 12:00 and 16:30. This was done to limit the influence of time of day which could affect cortisol levels. For female participants, the second and third session were scheduled during the luteal phase of their cycle, in order to prevent hormonal influences (Kirschbaum et al., 1999).

Questionnaires

During the first session, the participant filled out eight different questionnaires: the Apathy Motivation Index (AMI), the Snaith-Hamilton Pleasure Scale (SHAPS), the Need for Cognition questionnaire, the Multidimensional Fatigue inventory (MFI), Beck's Depression Inventory (BDI-II), the behavioural inhibition/avoidance scale (BIS/BAS), the Symptom Checklist 90 (SCL-90), and a 60-item version of the International Personality Item Pool (IPIP-NEO-60). This thesis was part of a larger study and the questionnaire data will not be analysed in this thesis, except for some data of the POMS questionnaire.

The AMI was used to measure apathy and motivation (Ang, Lockwood, Apps, Muhammed, & Husain, 2017). It measures three different factors: behavioural activation, social motivation, and emotional sensitivity. Additionally, the SHAPS was used to measure anhedonia and hedonia (Snaith et al., 1995). Furthermore, the tendency and enjoyment in thinking was measured using the Need for Cognition questionnaire (Cacioppo & Petty, 1982). Then, we used the MFI to measure different types of fatigue: general, physical, and mental fatigue, reduced motivation and reduced activity (Smets, Garssen, Bonke, & De Haes, 1995). Furthermore, the BDI-II was used to measure the severity of depression in participants (Beck, Steer, Ball, & Ranieri, 1996). The BIS/BAS scale differentiates between behavioural inhibition or punishment sensitivity and behavioural avoidance. In this questionnaire, behavioural avoidance is split up in four different subscales: pursuit of goals, desire for new rewards, and response to reward (Carver & White, 1994).

The SCL-90 was used to assess nine subscales – somatization, obsessive-compulsive behaviour, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety,

paranoid ideation, and psychoticism - in the past week (Blaszczynski & McConaghy, 1988). The IPIP-NEO-60 was used to measure five scales: neuroticism, extraversion, agreeableness, conscientiousness, and openness. Each of these scales consists of six subscales (Maples-Keller et al., 2017).

In order to assess their subjective stress, the participants filled in the adapted POMS questionnaire three times in both sessions: once before entering the scanner, once after the stress or control procedure (during the acquiring of the saliva sample), and once after the fourth block when they left the scanner. This questionnaire measures five distinct scales: anger, depression, fatigue, vigour, and tension-anxiety. The POMS questionnaire is scored on a scale from 0 to 4.

Saliva collection and analysis

To measure the objective stress, four saliva samples were collected in both the stress and control sessions. The first sample was collected right before the stress or control procedure (t = 0 min). The second sample was collected after the stress or control procedure (t = 15 min). The third sample was collected after block one (t = 30 min). The fourth sample was collected after block four (t = 75 min). See Figure 2B for an overview. Analysis of the cortisol and alpha-amylase levels in the saliva samples was performed according to Rohleder et al. (2006). This analysis was performed by the lab of Dr. C. Kirschbaum at the Technical University of Dresden.

Scanner preparation

During the MRI scanning of the stress and control sessions, a series of physiological measures and eye-tracking were recorded. An amplifier (brainamp ExG MR) from Brainproducts was used to measure heart rate, respiration and skin conductance. Heart rate was measured using a clip (Blood Pulse Sensor; Brainproducts) attached to the ring finger of the left hand of the participant. A glove was used to keep the hand of the participant warm. For the respiration, a belt with a sensor (Respiration Belt MR; Brainproducts) was attached around the waist of
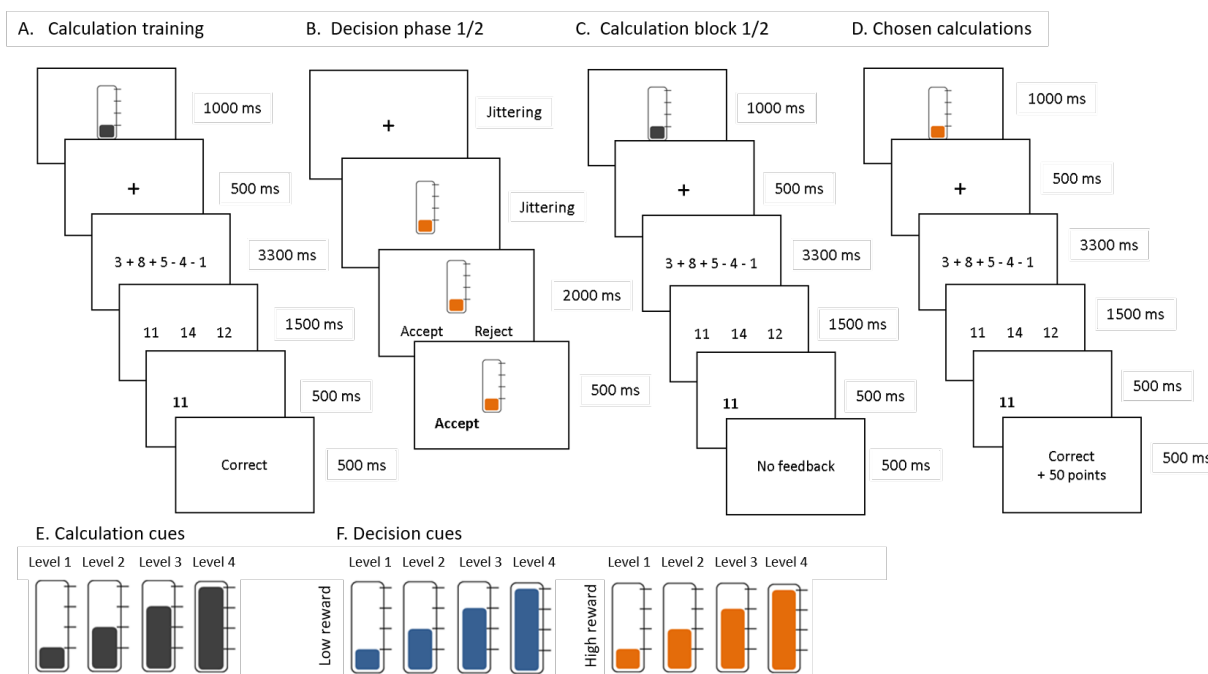
Figure 3. The layout of the tasks. A. The training done in the first session, and at the start of the second and third session. B. The first and second choice blocks inside the scanner during the second and third sessions. C. The calculation blocks inside the scanner during the second and third sessions. D. The calculations during the final part of the second and third sessions; these were done outside of the scanner. E. The cues shown during the calculation blocks. The levels indicate the difficulty of the upcoming calculation. F. The cues shown during the decision blocks. Blue coloured cues indicate that, when participants accept the calculation and answer correctly, they will receive a low reward, while orange coloured cues indicate a high reward.

the participant. In order to measure the skin conductance, two electrodes (B18-MR2-LSR-1A20g/AgCl Sintered Multitrode with 6 mm opening, MR Adapted) were attached to the index and middle finger of the left hand of the participant using conductive gel. The data was recorded using Brainvision recorder. Furthermore, pupil size was recorded during the task using the 'Eyelink 1000' (version 1.5.0, Eyelink). During the pupil size recordings, the lights in the scanner room were turned off.

Stress and control procedure

Acute stress was induced using an adapted version of the SECPT procedure (Schwabe et al., 2008), named alpha-SECPT. For this procedure, a researcher entered the room whom the participant had not seen before, wearing gloves and a lab coat. The procedure started with the participant putting their foot in a bucket of ice water (2 °C) for three minutes. The participant was instructed not to move or speak and to keep looking towards the ceiling throughout the procedure. The participant was informed that they could take their foot out, but only if it became truly unbearable. The researcher remained in the room looking at the participant the whole time. During the second part of the procedure, the participant was asked to recite the alphabet, alternating from going backwards and forwards, one letter at a time (i.e., z, a, y, b, x, c etc.). During this procedure, the same researcher as before was present, who told the participant to speed up if they took too long before answering, or start over if they were incorrect. The participant performed this task for three minutes. Afterwards, the researcher said that the task was over and acquired the second saliva sample.

The control procedure also consisted of two parts. An experimenter whom the participant had previously met entered the room and started putting the foot of the participant in a bucket of room temperature water (25 °C) for three minutes. Then, the participant was asked to normally recite the alphabet a few times. Any mistakes made during this task were ignored by the experimenter. After three minutes, the researcher told the participant that the task was over and took the second saliva sample.

Experimental tasks

Participants performed a calculation training task at the beginning of each session (outside the scanner; days 1, 2, and 3), a decision-making task (in the scanner; two blocks on day 2 and 3), a calculation reminder task (in the scanner; two blocks on day 2 and 3), and a final calculation task (outside the scanner; day 2 and 3). Each calculation consisted of four subsequent additions or subtractions. Difficulty of each calculation was manipulated by varying the amount of carrying or borrowing needed (one carrying/borrowing = difficulty level one, four carrying/borrowing needed = difficulty level four). For example, a level three difficulty calculation could look like '6-1+7-8+9'. This method has proven effective in earlier studies (Vassena et al. 2019, Vassena et al. 2014). All tasks are displayed in Figure 3.

Calculation training task

The calculation training (Fig. 3A) consisted of 100 trials and took around 20 minutes. Each training trial started with the fixation cross. Then, an indicator of the difficulty appeared on the screen in the form of a thermometer, with four possible levels (see Fig. 3E for an overview of the used cues). The participant was instructed that the more the thermometer was filled, the more difficult the following calculation would be. This thermometer was displayed for 1 second. Then, the fixation cross was displayed for 500 ms. Thereafter, the calculation was shown for 3300 ms. Following this, the calculation was replaced by three possible answers. The participant had 1500 ms to choose one of the answers. After they responded, or after 1500 ms passed, feedback was provided. After 500 ms, the next trial began.

Scanner task

During both the stress and control sessions (day 2 and 3), the participants performed four blocks in total: two blocks of the decision-making task, alternating with two blocks of the calculation reminder task. The decision-making task measured effort-based decision-making. The calculation reminder task measured the potential effect of stress

on accuracy. This task was named 'calculation reminder' as the participants were told that the purpose was to remind them of the meaning of each difficulty level.

Each session started with a calculation training. Decisions (Fig. 3B) and calculations (Fig. 3C) were presented afterwards. The choices started with a fixation cross for a jittered time (3-5 seconds, average 4 seconds), followed by a cue that appeared on the screen for a jittered time (3-5 seconds, average 4 seconds). This cue was either an orange thermometer, indicating a high reward (50 points), or a blue thermometer, indicating a low reward (40 points). As in the training, the more the thermometer was filled, the more difficult the calculation would be (see Fig. 3F for an overview of the different cues). The participants were instructed beforehand on the meaning of these cues. Then, the words 'accept' and 'reject' appeared on the screen for 2000 ms, or until the participant selected one of them. 'Accept' was displayed half of the time on the right and half of the time on the left side. Participants were instructed to accept trials that they considered worth the effort based on the promised reward. They were told that half of their choices would randomly be selected and that they would receive those trials to perform at the end of the session outside of the scanner. They would only receive the corresponding reward if the calculation was performed correctly during this final phase at the end of the session. If the participant rejected the trial, they would get a very easy calculation instead, but receive only 30 points if they answered the calculation correctly. The points were converted to a monetary bonus reward at the end of the experiment. Their choice remained on the screen for 500 ms, or they received feedback if they were too late. Then, the next trial started. If they were too late, the trial was appended to the end of the block.

The calculation trials also started with a fixation cross for 500 ms. Then, the thermometer was displayed for 1000 ms, followed by a fixation cross, that appeared on the screen for 500 ms. After that, the calculation appeared on the screen. After 3300 ms, three possible answers were displayed. They had 1500 ms to choose one of the answers. Afterwards, they received either no feedback,

or the message 'too late' if they were too late for 1000 ms.

Chosen calculations

After the decision-making task and the calculation reminder task in the scanner, the participant performed the chosen calculations (Fig. 3D). These were presented to the participant in the same way as the practice calculations from phase one, except that the provided feedback was not only 'correct' or 'incorrect', but also stated the amount of points received. Half of the trials from the decision-making block were randomly selected. For each of these trials, if they were accepted, the participant got a calculation of the shown difficulty, and received the shown reward if they responded correctly. If they responded incorrectly, no reward was received. If the participants rejected the calculation, a very easy calculation (e.g., '2+0+0+0+0') was presented. Upon correctly answering this calculation, the participant got 30 points. The participant was not aware of the exact value of one point in money, but they were told they could receive a maximum of 20 euros as a bonus for their performance.

Data analysis

This thesis focused on a subset of the collected data. Heart rate was analysed to ensure that the stress induction was successful. Behavioural data were analysed to test for behavioural effects of stress on effort-based decision-making. Furthermore, the eye-tracking data during the task were analysed as a putative index of NA release. Functional magnetic resonance imaging (fMRI) data were analysed to investigate the role of prefrontal cortex in effort-based decision-making under stress. This was done by examining the effect of effort and reward at the whole brain level during decision-making under control as compared to stress. Further, we extracted neural activity from a-priori defined ROIs of MPFC and DLPFC. Two ROI analyses were reported. The first analysis used functional ROIs based on the neural activity during the calculation reminder task, and specifically used the activity during the effort coding contrast (see the ROI section below for details) to test for the effect of stress

during decisions. The second analysis used an ROI based on previous studies of effort-based decision-making to test the effect of stress during both decision and calculation performance.

Heart rate analysis

To test the effectiveness of the stress induction, the heart rate of the participants was measured during scanning. These data were preprocessed using the Matlab toolbox Brainvisioncoverter. Afterwards, HERA (a Matlab toolbox) was used to calculate the interbeat intervals (IBI) for all participants. The visual artefact removal function of this toolbox was used to remove all artefacts where the heart rate could not be reliably measured. Then, the markers for the trials were added to these IBIs using the onsets generated for the MRI analysis. As previous research showed that stress causes an increase in heart rate, and therefore a decrease in IBI as well as a decrease in heart rate variability (Shapiro et al., 2000), three measures of interest were used to test the effectiveness of stress induction.

First, the first block after either stress induction or control was analysed by itself. These blocks were divided into four intervals of equal length. The average IBI was calculated on all of these intervals, for both stress and control. An analysis of variance (ANOVA) on the average IBI was conducted, with the main factors session type (stress or control) and interval (first, second, third or final part of the block), using session order (stress first or control first) as a between-subjects measure. Second, heart rate variability was measured. This was done by calculating the root mean square of successive IBI differences (RMSSD) on each interval. This measure calculates the mean square differences of successive IBIs, and takes the square root of this value. An ANOVA on these data was performed, with the main factors session type and interval, using session order as a between-subjects measure. Third, the average IBI was calculated from the moment the cue appeared on the screen until three seconds after the trial started. This was done for every different trial, both during the decision-making trials and the calculation trials.

Two ANOVAs were performed on the trial-by-trial IBI to determine possible effects of stress, effort, and reward on the heart rate during the task: one on the decision-making trials and one on the calculation trials. The ANOVA on the decision-making trials examined the following factors: session type (stress or control), block (one or two), effort level (very easy, easy, hard, very hard), and reward level (low reward, high reward). Session order (stress first or control first) was used as a between-subjects factor in this ANOVA. The ANOVA on the calculation trials had the following factors: session type (stress or control), block (one or two), effort level (very easy, easy, hard, very hard). Session order (stress first, control first) was also used as a between-subjects factor in this ANOVA. Post-hoc analysis was done on significant results using Bonferroni-correction. In t-tests, Cohen's d was used as a measure for effect size. In ANOVAs, partial η^2 was used as a measure for effect size.

Behavioural data analysis

Willingness to engage in effort was measured through acceptance rate at the decision-making task. Reaction times of the decisions were also recorded. The effect of stress on the ability to perform the task was measured during the calculation task for which accuracy and reaction times were recorded. Because the decisions and accuracy are dichotomous variables (accept/reject, correct/incorrect), generalized linear mixed models (GLMM) using a binomial family and logit link function were performed on this data using R (version 3.5.2) and the lme4 package (Bates, Mächler, Bolker, & Walker, 2015). Three different optimizers were used, 'bobyqa', 'Nelder Mead', and 'optimx', in order to reduce convergence problems. Results of any of these optimizers that find no convergence issues were reported. Reaction times were first transformed by the function log(1/x) to decrease violations of the normality assumption (normality was checked for the averages per condition with the Shapiro test, and normality for the choices (statistic = 0.997, p = .18) was found. Additionally, near normality for calculations (statistic = 0.991, p = .01) was found). Although this was not completely normally distributed, the transformation was an improvement over

using the regular mean for the calculation trials (statistic = 0.983, *p* < .001). Afterwards, a linear mixed model (LMM) was used to test for significance. Furthermore, to test whether this effect was influenced by other factors, the analyses were repeated including different covariates. The covariates of interest were task proficiency, subjective stress and objective stress.

Task proficiency was measured using the average accuracy on the training trials of all three days for each participant. Covariates for subjective and objective stress were included to take inter-individual variability in subjective stress experience and objective stress into account. Subjective stress was measured using the difference in tension and depression scores from the POMS after stress and control. Objective stress was supposed to be measured using salivary cortisol. However, due to the Covid-19 lockdown, it became impossible to further analyse the collected samples. As of the moment of writing this thesis, only the saliva samples for 12 participants have been analysed. Therefore, it was decided to not include the cortisol analysis in this thesis, and include the heart rate during the first block of task post-stress induction as a plausible physiological index of the individual stress levels.

The GLMMs for the decision-making data included effort level, reward level, session type, their interactions, block and the covariate as fixed effects. First, a model containing a random slope and intercept for all fixed variables was used (as recommended by Barr, Levy, Scheepers, & Tily, 2013). If this model did not converge, only a random slope for effort level, reward level, and session type was included in order to reduce the complexity of the model. Subject number was also included as a random factor. Finally, a model containing all covariates was run. In order to measure effect sizes for the GLMMs, the log odds ratio (LO) was reported.

The GLMMs for the calculation task used effort level, block, session type, effort level x session type, and the covariate as fixed variables. First, a model containing both random slope and intercept for all fixed variables was used. In case of non-convergence, a model only containing random slope for effort level, session type, and the covariate was included. Subject number was also included as a random factor.

Pupil size analysis

In order to assess putative noradrenergic levels, pupil size was measured. Eye-tracking data were analysed using a custom Python script (Python version 2.7). First, the average pupil size was extracted for each trial (starting from the moment the thermometer appeared until a response was given). Eye blinks were excluded. These values were z-scored to the data from the same block type (i.e. calculations or decision-making). Data were exported to SPSS where two ANOVAs were conducted. The first ANOVA was done on the calculation task, containing session type, effort level and block as within-subjects factors, and session order as between-subjects factor. The second ANOVA was calculated on the decision-making data, using session type, effort level, reward level, and block as within-subjects factors, and session order as between-subjects factor.

MRI data collection and preprocessing

Functional MRI data was acquired on two 3T Siemens MRI scanners (Prisma and Prismafit), located on the same site and using identical sequences. In the first session, a standard MPRAGE anatomical scan was collected using a 32-channel head coil. This yielded 224 slices (voxel size: 0.8x0.8x0.8 mm, FoV = 256 mm, TR = 2200 ms, TE = 2.64 ms, flip angle: 11 degrees). After this, an interleaved gradient echo scan was conducted to measure the VTA, giving 176 slices (voxel size: 0.8x0.8x0.8 mm, FoV = 230 mm, TR = 46.00 ms, TE = 6; 14.1; 22,2; 30,3; 10.05; 18.15; 26.25; 34.35, flip angle: 20 degrees, centred at L = 0, A = 15, H = 4). Additionally, two different echo planar imaging scans were used to acquire data from the LC. This scan was centred on the LC position found in the anatomical scan (default: R = 0.1, P = 1.2, F = 32.9 mm) and rotated so that the scan was perpendicular to the fourth ventricle. One scan yielded 16 slices (voxel size: 0.2, 0.2, 3.0 mm, slice thickness: 3.0 mm, FoV = 220 mm, TR = 1870 ms, TE = 12 ms, flip angle = 120 degrees). The second scan was the same, except for the location, which was 1.5 mm above the first scan. These two scans were alternated three times each,

for a total of six scans. These scans together took about 45 minutes.

During the stress and control sessions, functional images were acquired. Two decision-making and calculation runs were performed. The decision-making runs gave 66 slices per scan, with about 790 scans per block (voxel size: 2.0x2.0x2.0 mm, FoV = 210 mm, TR = 1000 ms, TE = 34.00 ms, flip angle: 60 degrees). Calculation runs gave 66 slices per scan, with about 450 scans per block (voxel size: 2.0x2.0x2.0 mm, FoV = 210 mm, TR = 1000 ms, TE = 34.00 ms, flip angle: 60 degrees). All functional runs were interleaved multi-band, with multi-band factor 6.

In order to reach steady state magnetisation, the start of the task was synced with the fifth volume. Hence, the first four volumes were discarded in the analysis. The data was preprocessed using fMRIprep (version 20.0.6, Esteban et al. 2018), using Nipype (version 1.4.2, Gorgolewski et al., 2011). Here, the anatomical data is preprocessed using skull stripping, and segmented to create a brain mask (Zhang et al. 2001). These data were then normalized. The functional data was co-registered to this anatomical data. Head-motion parameters were estimated using FSL (version 5.0.9, mcflirt, as described by Jenkinson et al. 2002). On the preprocessed images, smoothing and AROMA (Pruim et al. 2015) were applied. Images with a high framewise displacement (FD) or DVARS value (as described by Power et al. (2014)) were marked as motion outliers (i.e. with an FD larger than 0.5, or DVARS larger than 1.5). Due to the low TR of the sequence, no slice time correction was applied. For more details on fMRIprep, see the supplementary methods (available online).

fMRI analysis

The fMRI data were analysed using a general linear model (GLM) approach. Two first-level GLMs were generated (one for the decision-making and one for the calculation blocks). The decision-making GLM contained eight event-related regressors per block; one for each different effort by reward combinations, an additional three regressors to measure the responses, one for the right button, one for the left button, and one for a late response. In the calculation GLM, six different regressors

were measured per block; one for each of the four different difficulty levels, one for incorrect trials, and one for responses that were too late. In both analyses, the trials that were too late were modelled as noise in a separate regressor.

At the second level, parametric effort contrasts (very easy: -1.5, easy: -0.5, hard: 0.5, very hard: 1.5), quadratic effort contrasts (very easy and very hard: -1, easy and hard: 1), and a low versus high effort contrast (very easy and easy: 1, hard and very hard: -1) were made for the decision-making data. Furthermore, reverse contrasts were made for each of these contrasts by multiplying the contrasts with -1. Additionally, a contrast was made for high versus low reward in order to identify reward-related regions in the decision-making data. To investigate the effect of stress, each of the contrasts in the control condition was compared to the stress condition (both stress > control and control > stress). A voxel level threshold of p = .001 (uncorrected) was applied with a cluster-level Family Wise Error (FWE) correction for multiple comparison of p = .05. For the calculation analysis, the same effort contrasts were made using the same thresholds.

For the Region-of-Interest (ROI) approach, we performed two analyses. For the first analysis, we selected clusters that encode effort during the calculation reminder task. This was done by testing which regions are more active with increased effort during the calculation reminder task. Regions in the MPFC (including dACC) and DLPFC are of interest here, as they are known to have a role in effort-based decision-making (Vassena et al., 2017; Asci et al., 2019; Porter et al., 2019). Furthermore, to do a preliminary analysis of the effects of stress on the SN, we also selected clusters from the insula for the ROI analysis. The ROIs obtained from the calculation reminder task were then used to extract neural activity during the decision-making task (avoiding circularity of inference).

The second analysis was aimed at testing activity under stress in both the decision-making and calculation phase. Hence, we selected an a-priori ROI of the MPFC based on previous studies on effort coding (Botvinick, Huffstetler, & McGuire, 2009; Bush et al., 2001), and completely contained the dACC part of the FIND template (Shirer,

Ryali, Rykhlevskaia, Menon, & Greicius, 2011). The ROI used for the MPFC was centred on the MNI coordinates (2, 21, 40). All ROIs were defined as a sphere with an 8 mm radius centred around the peak voxel of the observed cluster. For these ROIs, percent signal change was extracted using the MARSBAR toolbox (Brett et al., 2002) for each separate regressor in the decision-making analysis. Percent signal change scores per condition were subjected to an ANOVA to analyse the effects of effort, reward, block, session order and session type on the activation of these ROIs.

Results

Heart rate analysis

The data from three participants were excluded due to excessive noise and poor data quality, which made the analysis not possible. The final sample for the RMSSD and first block IBI included 22 participants. The ANOVA on the first block RMSSD yielded a significant main effect of time after onset (F(2.19, 43.73) = 10.23, partial η^2 = .34, p < .001), which can be explained by a decrease in RMSSD after the first quarter of block one (p-hoc t-tests: 1 > 2: T(21) = 4.82, Cohen's d = 0.57, p < .001; 1 > 3: T(21) = 3.77, Cohen's d = 0.55, p = .001; 1 > 4: T(21) = 2.36, Cohen's d = 0.32, p = .03; 4 > 2: T(21) = 2.53, Cohen's d = 0.26, p = .02; 4 > 3: T(21) = 2.18, Cohen's d = 0.23, p = .04, Fig. 4A). There was a significant effect of session order (F(1, 20) = 5.10, partial η^2 = .20, p = .04), indicating that the heart rate variability was higher for participants that had the control session first. Contrary to what was expected, no significant main effect of session type was observed (F(1, 20) = 3.18, partial η^2 = .14, p = .09), although we found a trend toward lower RMSSD in the stress session. There was a significant interaction effect of session type x session order (F(1, 20)= 5.45, partial η^2 = .21, p = .03), but post-hoc t-tests did not reveal any significant effects. However, we observed a trend for a decrease in RMSSD for the second and third quarter of the first block for the participants that had the stress session first compared to the participants that started with the control session. The time after onset x session type x session order interaction (F(1.83, 36.54) = 4.15, partial η^2=.17, p = .03)
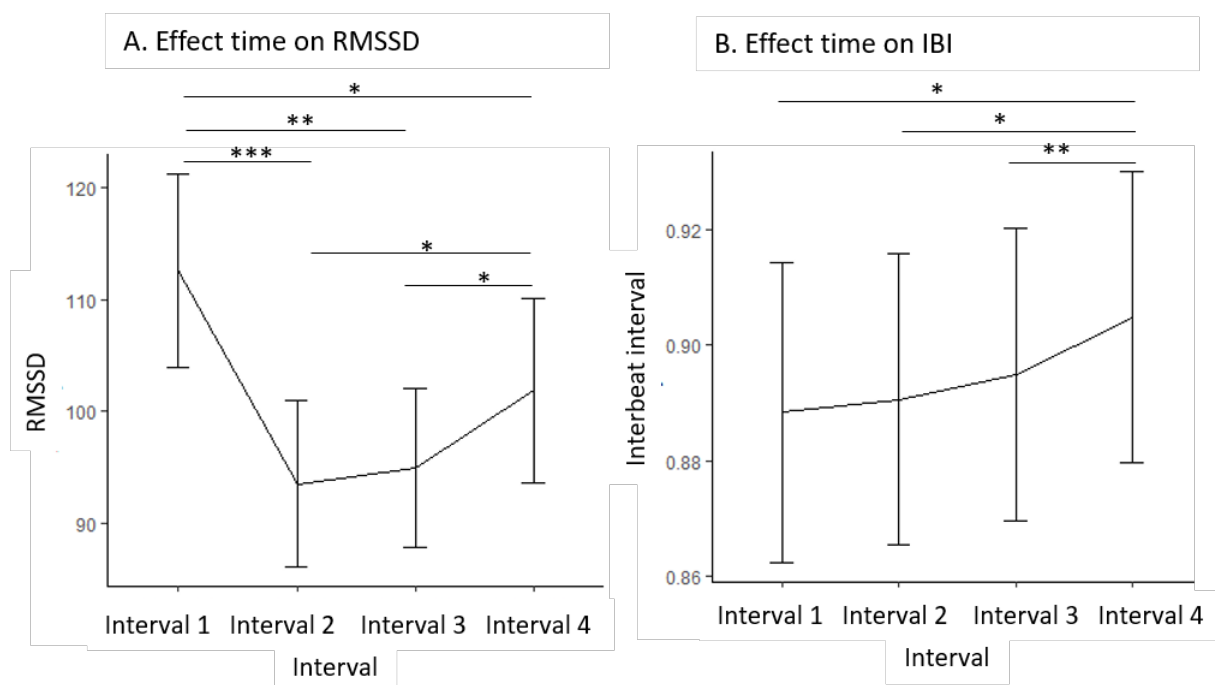

Figure 4. A. The effect of time on the root mean square of successive IBI differences (RMSSD). The first block has been divided into four equally long intervals. During the first interval, the RMSSD was significantly higher than during the other three intervals. During the fourth interval, the RMSSD was significantly higher compared to intervals two and three. B. Effect of time on the interbeat interval. The interbeat interval during the final interval was significantly higher compared to the other three intervals. * p < .05, ** p < .01, *** p < .001.

was also significant. A post-hoc t-test on the interactions found a significantly lower RMSSD in stress, for participants that started with the control condition, for the first interval (T(11) = -2.90, Cohen's d = -0.74, p = .01) and fourth interval (T(11) = -2.61, Cohen's d = -0.85, p = .02). A trend for lower RMSSD in stress was found in the second interval (T(11) = -2.05, Cohen's d = -0.58, p = .07).

The analysis of the IBI yielded a significant main effect of time after onset (F(1.69, 33.84) = 4.92, partial η^2 = 0.20, p = .02, Fig. 4B), giving a lower average heart rate at the final interval compared to the other intervals (4 < 1; T(21) = 2.92, Cohen's d = 0.15, p = .008, 4 < 2; T(21) = 3.75, Cohen's d = 0.13, p = .001, 4 < 3; T(21) = 4.41, Cohen's d = 0.09, p = < .001). The interaction between time after onset x session type (F(2.16, 43.26) = 4.93, partial η^2 = .20, p = .01), and time after onset x session type x session order was also significant (F(2.16, 43.26) = 5.58, partial η^2 = .22, p = .006). However, post-hoc analyses found no significant differences between stress and control for constant time after onset and session order.

The ANOVA on the average IBI during each decision-making trial found a main effect of block (F(1, 20) = 8.29, partial η^2 = .29, p = .009), indicating a higher heart rate in the first block compared to the second. A significant interaction effect of effort x block x reward was also found (F(3, 60) = 2.97, partial η^2 = .13, p = .03). Post-hoc analysis found a significant higher IBI in block two compared to one in the low reward condition, for very easy (T(21) = 3.73, Cohen's d = 0.26, p = .001), easy (T(21) = 2.36, Cohen's d = 0.17, p = .03), and very hard (T(21) = 2.45, Cohen's d = 0.20, p = .02) trials, and in the high reward condition for hard trials (T(21) = 3.68, Cohen's d = 0.26, p = .001). Furthermore, a higher IBI for high reward compared to low reward in the very hard trials of the first block was found (T(21) = -2.49, Cohen's d = -0.10, p = .02). Additionally, an effect of type x block x effort was found (F(3, 60) = 2.86, partial η^2 = .13, p = .04). However, follow up tests did not give any significant effects. Surprisingly, no effect of session type was found in either the decision-making (F(1,20) = 0.06, partial η^2 <.01, p = .82) or calculation trials (F(1, 20) = 0.60, partial η^2 = .03, p = .45). In the calculation trials, no significant effects were found.

Behavioural analysis: Decision-making

The behavioural data were analysed for all participants. No additional participants were excluded, given that every participant showed a sufficiently variable choice behaviour (i.e. No subject accepted or rejected everything) and an average performance level above chance (M = 0.72, SD = 0.15, chance level = 0.33). Therefore, the behavioural analysis was conducted for 25 participants.

First, the acceptance rate during decision-making was analysed. This analysis investigated the effect of stress on decision to engage in effort as a function of difficulty level and reward level. As expected in this task, there was a main effect of effort (z = -8.35, LO = -3.06, p < .001 Fig. 5A) and reward (z = 10.02, LO = 1.73, p < .001 Fig. 5B). As expected, participants accepted harder trials less often, and large reward trials more often. Furthermore, there was a significant effect of session type (z = 2.02, LO = 0.23, p = .04 Fig. 5C), indicating that participants accepted trials less in the stress condition compared to the control condition. In addition, there was a trend towards significance in the interaction effort x reward x session type (z = 1.70, LO = 0.072, p = .09), indicating an effect of stress on both reward and effort. However, post hoc t-tests did not find a significant interaction between stress and control for any level of reward or effort.

Accuracy as covariate

Because of the large individual variability in baseline accuracy performance of the calculation task, we tested whether calculation accuracy during the training was associated with decisions. To this end, the previous analysis was repeated including training accuracy as a covariate. Training accuracy was defined as the average accuracy score of the three training phases. As expected, training accuracy had a significant impact on acceptance rate (z = 3.59, LO = 4.55, p < .001), showing that participants that were better at the training calculations accepted more often to engage in effort. As in the previous analysis, main effects of effort (z = -8.35, LO = -3.06, p < 0.001), reward (z = 10.07, LO = 1.72, p < .001), and session type were found (z =
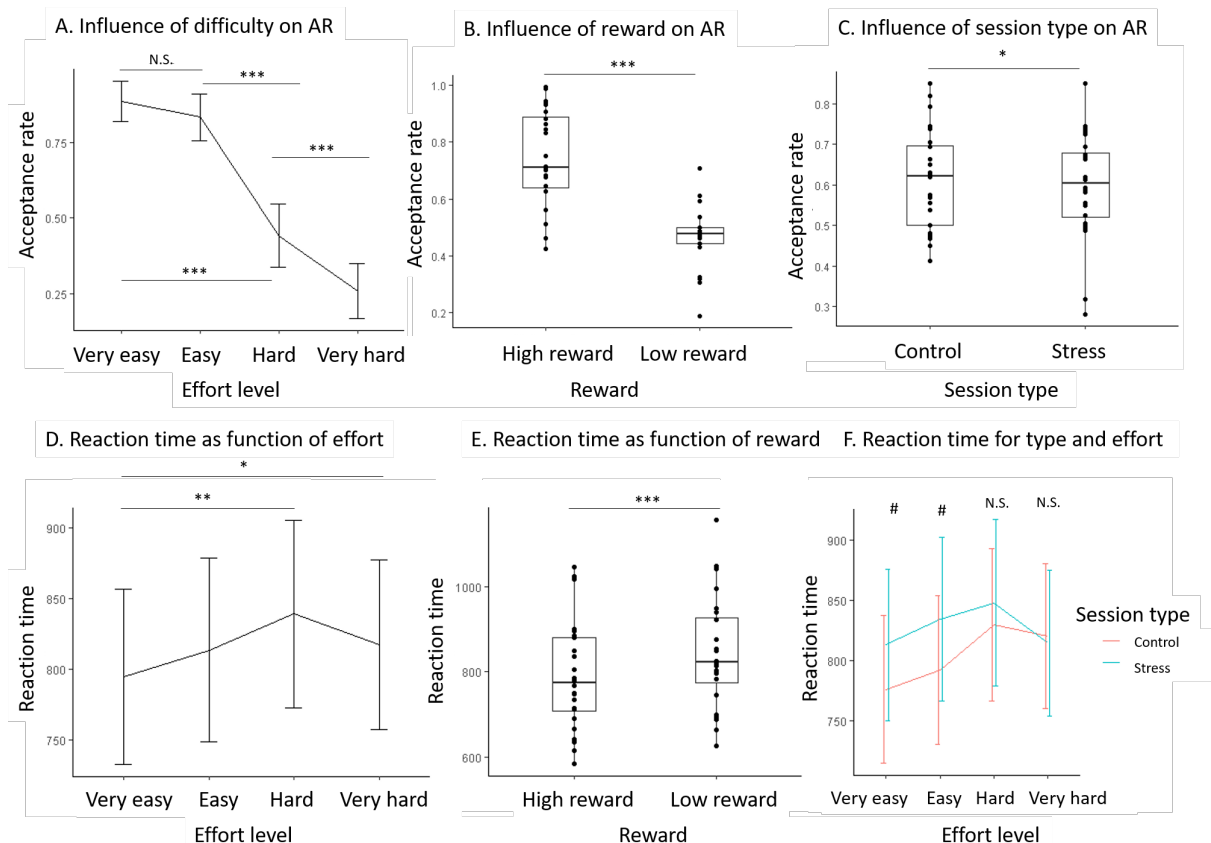
Figure 5. Behavioural effects in the decision-making trials. A. The acceptance rate in the decision-making trials as a function of difficulty. There was no significant difference between the very easy and easy trials. But starting from the easy trials, there is a significant decrease of acceptance rate. The error bars indicate the mean +/- SEM. B. The influence of reward on acceptance rate. We can see that the high reward trials were accepted significantly more often compared to the low reward trials. C. The effect of session type on acceptance rate. We found that participants accepted less trials in the stress condition compared to the control condition. D. The influence of difficulty level on reaction time during the decision-making trials. Both hard and very hard trials were performed significantly slower compared to very easy trials. E. Reaction time as a function of reward. We can see that high reward trials were performed significantly faster compared to low reward trials. F. Reaction time as a function of session type and effort level. We can see that there was a trend for faster reaction times in the control session compared to the stress session in the very easy and easy trials, while this trend was not found for the hard and very hard trials. # p < .1, * p < .05, ** p < .01, *** p < .001.

2.03, *LO* = 0.23, *p* = .04). Again, a trend for significance in the interaction effort x reward x session type was found (*z* = 1.66, *LO* = 0.07, *p* = .10).

Subjective stress as covariate

Generally, there is substantial variability in the subjective experience of stress; some participants might have thought the stress induction we perform is more of a challenge than a stressful event. To account for this variability, we repeated the previous analysis including differences in the self-report scores at the POMS questionnaire for tension and depression after stress and control. First, we included the POMS depression score as a covariate. This analysis confirmed the main effects of effort (*z* = -8.35, *LO* = -3.06, *p* < .001), reward (*z* = 10.02, *LO* = 1.73, *p* < .001), and session type (*z* = 2.02, *LO* = 0.23, *p* = .04). The trend for significance in the interaction effort x reward x session type was confirmed (*z* = 1.70, *LO* = 0.07, *p* = .09). No significance was found in the depression subscale (*z* = 0.09, *LO* = 0.03, *p* = .93).

Second, the POMS tension score was included as a covariate. This analysis found a

significant effect of the POMS tension score on acceptance rate (z = 3.24, *LO* = 0.87, *p* = .001), indicating an increase in acceptance rate with higher tension. Furthermore, it confirmed the main effects of effort (z = -8.34, *LO* = -3.06, *p* < .001), reward (z = 10.06, *LO* = 1.73, *p* < .001) and session type (z = 2.04, *LO* = 0.23, *p* = .04). Furthermore, a trend for significance in the interaction effort x reward x session type was confirmed (z = 1.68, *LO* = 0.07, *p* = .09).

IBI as a covariate

The physiological response to stress is known to vary across individuals. This is commonly measured via cortisol sampling. However, due to the COVID-19 pandemic, cortisol from only 12 participants has been analysed. Hence, we computed an alternative measure of objective stress based on heart rate changes: the difference in average IBI. This measure was included as a covariate to control for the difference in stress experience in the first quarter of the first block of both the stress and control session. In order to avoid convergence errors in the model, we replaced the session type variable with IBI as both a fixed effect and random effect.

This analysis confirmed the effects of effort (z = -8.48, *LO* = -2.97, *p* < .001) and reward (z = 10.42, *LO* = 1.66, *p* < .001). Furthermore, an interaction effect of effort x reward x IBI was found (z = 6.44, *LO* = 2.73, *p* < .001). Running a post-hoc GLMM for every effort level revealed a significant interaction of IBI and reward on acceptance rate in the very hard trials (z = 4.51, *LO* = 11.07, *p* < .001). A higher IBI in the high reward condition caused an increase in acceptance, while a higher IBI in the low reward condition caused a decrease in acceptance.

Full model

The model containing all covariates for the behavioural analysis confirmed the effects of effort (z = -8.52, *LO* = -2.97, *p* < .001) and reward (z = 10.46, *LO* = 1.66, *p* < .001). Additionally, main effects of accuracy (z = 2.78, *LO* = 3.33, *p* = .006) and tension (z = 2.64, *LO* = 0.80, *p* = 0.008) were found. Furthermore, the interaction effort x reward x IBI (z = 6.51, *LO* = 2.76, *p* < .001) was confirmed.

Summary for acceptance rate during decision making

Concluding, in the decision-making trials, significant effects of effort and reward were found. Furthermore, both accuracy and the tension subscale of the POMS had a significant influence on acceptance rate, both having a positive correlation with overall acceptance of trials.

Behavioural analysis: decision-making reaction times

The first Linear Mixed Model (LMM) found a significant main effect of effort (T(48) = -3.29, *p* = .002, Fig. 5D). Post hoc testing found that reaction times were faster for very easy trials compared to hard (T(24) = -3.52, Cohen's d = -0.32, *p* = .002), and very hard (T(24) = -2.24, Cohen's d = -0.18, *p* = .04) trials. There was also a main effect of reward (T(48) = 6.14, *p* < .001, Fig. 5E), indicating a faster reaction time in the high reward condition. A significant interaction effect of session type x effort was found (T(7488) = -3.20, *p* = .001, Fig. 5F), indicating a faster reaction time in the control session compared to the stress session, but only in the very easy and easy condition.

Accuracy as covariate

The LMM on reaction times for decisions, with accuracy as covariate found no effect of accuracy (T(30.1) = 0.01, *p* = .99), but confirmed the effects of effort (T(48.26) = -3.29, *p* = .002), reward (T(49.4) = 6.08, *p* < .001), and session type x effort (T(7493) = -3.20, *p* = .001).

Subjective stress as covariate

The LMM with the depression subscale of the POMS found a main effect of this subscale (T(18.55) = -3.58, *p* = .002), indicating a higher depression score caused overall slower reaction times. Furthermore, it confirmed the effects of effort (T(49.12) = -3.26, *p* = .002), reward (T(48) = 6.14, *p* < .001), and session type x effort (T(7491) = -3.20, *p* = .001). The LMM with the tension subscale of the POMS as covariate found a trend for the main effect of the tension subscale was found(T(29.97) = -1.92, *p* = .06), which could be an indicator

that participants reporting higher tension had slower reaction times overall. Furthermore, it confirmed the effects of effort ($T(48.7) = -3.28$, $p = .002$), reward ($T(48.26) = 6.12$, $p < .001$) and session type x effort ($T(7491) = -3.20$, $p = .001$).

IBI as a covariate

When using IBI as a covariate, no significant effect of IBI was found ($T(30.41) = -0.04$, $p = .97$). The analysis did confirm the effect of effort ($T(35.34) = -3.38$, $p = .002$), and reward ($T(41.61) = 5.45$, $p < .001$). However, it should be noted that this model gave a singular boundary error. Since two of the tested LMM methods gave very similar results, these results were reported.

Full model

The model containing training accuracy, both subscales of the POMS and the IBI as covariates gave a singular boundary error. Therefore, the results cannot be interpreted reliably.

Summary for decision-making reaction times

Concluding, for the reaction times, we found a faster reaction time with easier difficulty or higher reward. Additionally, participants with a higher depression rating reacted slower.

Behavioural analysis: calculation accuracy

This analysis was done to study the effect of stress on task performance. A main effect of effort was found ($z = -15.45$, LO= -0.56, $p < .001$, Fig. 6A), indicating a decrease in accuracy in the more difficult levels as expected ($1 > 2$; $T(22) = 5.30$, LO = 0.92, $p < .001$, $2 > 3$; $T(22) = 9.29$, LO = 1.75, $p < .001$, $3 > 4$; $T(22) = 3.16$, LO = 0.30, $p = .004$). This indicated that the difficulty manipulation was successful. No other significant main effects or interactions were found.

Accuracy as covariate

The analysis of the task accuracy, with training accuracy as a covariate found a main effect of training accuracy ($z = 16.70$, $LO = 5.71$, $p < .001$), indicating a better performance in the calculation task for participants that performed better on the training, as expected. The effect of effort ($z = -17.45$, $LO = -0.58$, $p < .001$) was confirmed.

Subjective stress as covariate

To account for the inter-individual variability in stress perception, we repeated the previous analysis including differences in the self-report scores of the POMS questionnaire for tension and depression after stress and control. Both analyses did not find a main
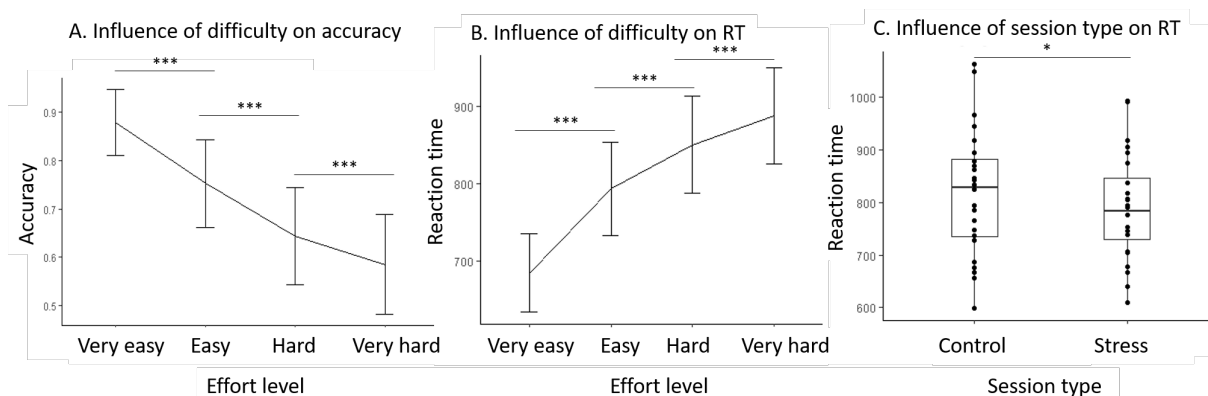

Figure 6. Effects in the calculation trials. A. The influence of difficulty on accuracy during the calculation trials. There was a significant decrease in performance with higher increasing level of difficulty. B. The influence of difficulty level on reaction time during the calculations. There was a significant increase in reaction time when the difficulty level increased. C. The influence of session type on reaction time in the calculation trials. We can see that participants performed significantly faster in the stress trials compared to the control trials. * p < .05,*** p < .001.

effect of the covariate (depression: z = 0.68, LO = 0.20, p = .50; tension: z = 0.65, LO = 0.13, p = .52), but confirmed the main effects of effort (depression: z = -15.52, LO = -0.56, p < .001; tension: z = -15.48, LO = -0.56, p < .001). Both analyses did not find any other significant effects.

IBI as a covariate

When including IBI as a covariate, a main effect of the covariate was found (z = 9.67, LO = 2.86, p < .001), indicating a better performance with increased IBI. Furthermore, the main effect of effort was confirmed (z = -10.36, LO = -0.56, p < .001).

Full model

When all covariates were included in the model, the model gave a singular boundary error (likely due to model complexity). Therefore, these results cannot be interpreted reliably.

Summary for the calculation accuracy

Concluding, we found a better accuracy in the calculation trials in easier calculations, and better accuracy for participants who also performed better in the training. Furthermore, a higher IBI correlated with a better performance.

Behavioural analysis: calculation reaction times

The first LMM on reaction time found a main effect of effort (T(47.92) = -12.87, p < .001). As expected, participants responded faster to easier calculations, and reaction time increased linearly with effort level. This confirmed that the difficulty manipulation was successful. (2 > 1; T(22) = 7.28, Cohen's d = 1.03, p < .001, 3 > 2; T(22) = 3.88, Cohen's d = 0.45, p < .001, 4 > 3; T(22) = 2.92, Cohen's d = 0.29, p = .008, Fig. 6B). An effect of session type was found (T(48.25) = -2.53, p = .01), suggesting a faster reaction time during the stress session compared to the control session (Fig. 6C).

Accuracy as covariate

The LMM on reaction time with accuracy as covariate found a significant effect of accuracy (T(33.63) = 5.56, p < .001), indicating a faster reaction time when the training accuracy was better. Furthermore, the main effect of effort (T(47.93) = -12.89, p < .001), and session type (T(48.25) = -2.52, p = 0.02) were confirmed.

Subjective stress as covariate

The LMM on the depression subscale of the POMS as a covariate found no main effect of the depression score (T(49) = -0.79, p = .43). This analysis confirmed the main effect of effort (T(48.43) = -12.80, p < .001) and session type (T(48.39) = -2.52, p = .02). The LMM on the tension subscale of the POMS found a significant effect of this subscale (T(33.98) = 2.19, p = .04), indicating a faster reaction time for participants that reported higher tension. Furthermore, it also confirmed the main effects of effort (T(48.19) = -12.85, p < .001) and session type (T(48.33) = -2.53, p = .01).

IBI as a covariate

In the LMM model using IBI as a covariate, no main effect of IBI was found (T(40.45) = 1.08, p = .29). However, a trend for the interaction effort x IBI was found (T(41.45) = -1.82, p = .08), indicating that participants with lower heart rate were particularly fast in easy trials. Furthermore, the main effect of effort (T(41.52) = -12.45, p < .001) was confirmed.

Full model

When all covariates were included in the model, the model gave a singular boundary error, so we cannot interpret the results from this analysis reliably. This again might have to do with the model containing all covariates being too complex for the amount of data that was included.

Summary calculation reaction times

Concluding, reaction times increased with higher difficulty levels and in the control session. Furthermore, both higher accuracy and tension were associated with an overall faster response time.

Pupil size analysis

In order to analyse the influence of stress effects on putative noradrenaline levels during effort-based decision-making, both the pupil size during the decision-making trials and the pupil size during the calculation trials were analysed. For this analysis, two participants had to be excluded due to the data of one session being corrupted, and five others had to be excluded due to noisy data in at least one of the blocks. First, an ANOVA was performed on the pupil size during the decision-making trials. Contrary to what was expected, no main effect of session type ($F(1,15) = 0.19$, partial $\eta^2 = 0.01$, $p = .67$) was found. A significant interaction effect of reward x session order was found ($F(1,15) = 8.16$, partial $\eta^2 = 0.35$, $p = .01$, Fig. 7A), indicating a larger pupil size in the low reward condition compared to the high reward condition in participants that had the control session first (post hoc t-test: $T(16) = 6.46$, Cohen's d = 4.08, $p < .001$). Unexpectedly, no significant interaction effect of either session type x reward ($F(1,15) = 0.81$, partial $\eta^2 = 0.05$, $p = .38$) or session type x effort ($F(3,45) = 0.90$, partial $\eta^2 = 0.06$, $p = .45$) was found.

Second, an ANOVA was done on the calculation trials. This ANOVA revealed a significant main effect of effort ($F(2.018, 32.294) = 11.38$, partial $\eta^2 = 0.42$, $p < .001$, Fig. 7B), indicating larger pupil size for increasing effort. Post hoc t-tests indicated that this effect was caused by a significant smaller pupil size in the very easy calculation trials and the other difficulty levels (very easy < easy: $T(16) = 5.65$, Cohen's d = 1.85, $p < .001$; very easy < hard: $T(16) = 5.87$, Cohen's d = 2.37, $p < .001$, very easy < very hard: $T(16) = 3.62$, Cohen's d = 1.52, $p = .002$). Contrary to the expectations, no significant main effect of session type was found ($F(1,16) = 1.04$, partial $\eta^2 = 0.06$, $p = .32$). Furthermore, the interaction effect of session type x effort ($F(3,48) = 2.05$, partial $\eta^2 = 0.11$, $p = .12$) was not significant.

MRI analysis

This analysis focused on effort and reward coding during decision-making, and effort coding during the calculations. First, the whole-brain results of the decision-making task and the calculation task are presented.

Second, the results of two ROI analyses are presented. The first ROI analysis employed the calculation task as an effort-coding localizer (i.e. a way to identify effort-sensitive regions). These regions were subsequently used as ROI to investigate effort coding during decision-making and under stress. From the regions that are coding for effort, only the regions that were hypothesized to be involved in
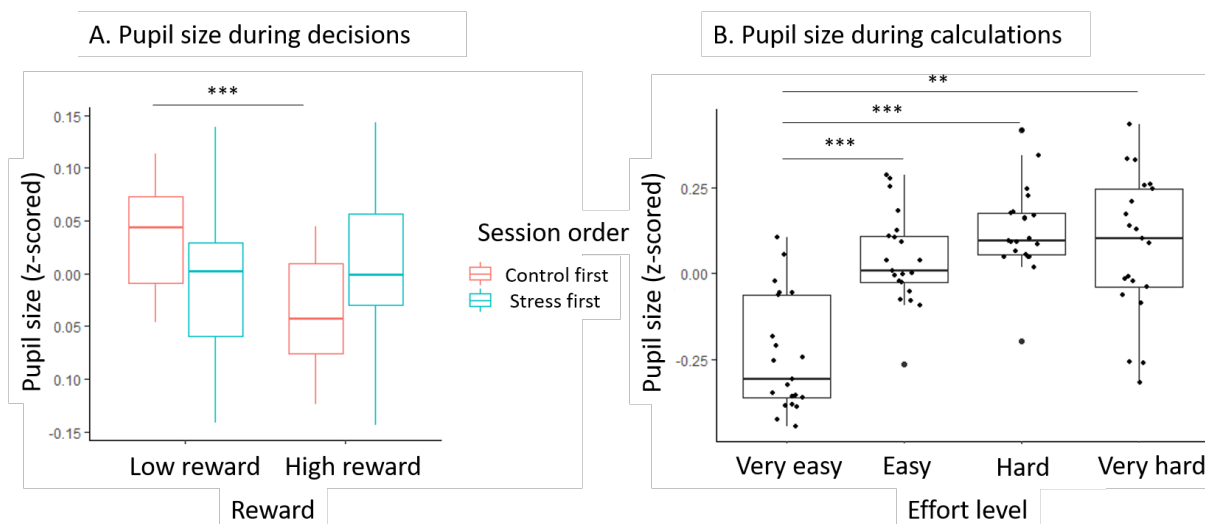

Figure 7. A. The effect of session order on the z-scored pupil size during decisions. No significant difference in pupil size was found for the participants that started with the stress condition, while the participants who started with the control condition had a significantly smaller pupil size in the high reward condition. B. The effect of effort level on the z-scored pupil size. The pupil size in the very easy condition was significantly lower compared to the other effort levels. ** p < .01,*** p < .001.
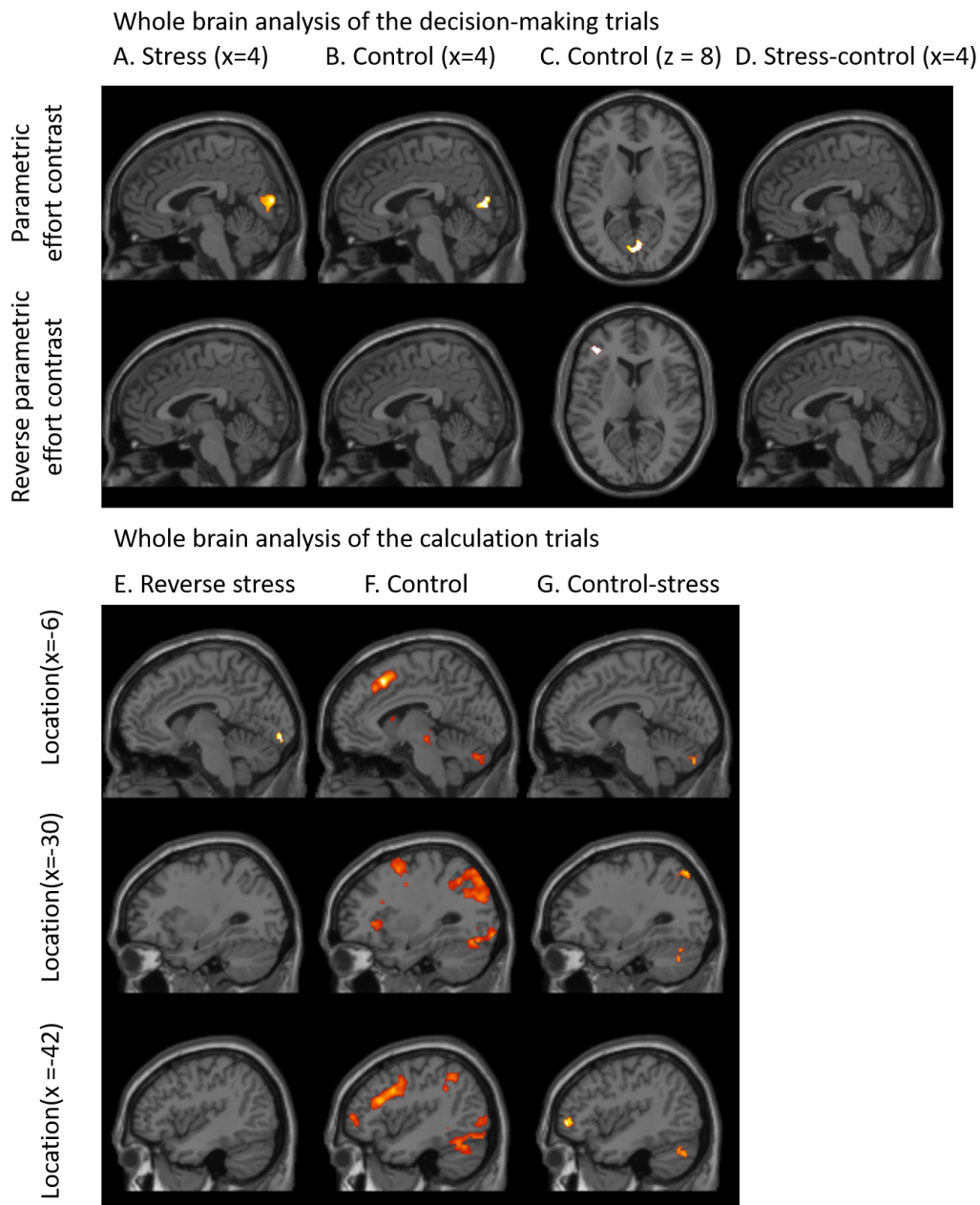
Figure 8. The whole brain activity for different contrasts at different locations. A-D. The whole brain activity during the decision-making trials. All contrasts were parametric effort (top row) and reverse parametric effort (bottom row). The clusters were generated by first taking voxels that had a voxel-wise significance of p < .001. Then, clusters were shown with at least 50 significant voxels were shown. A. The parametric and reverse parametric stress contrast. The only significant cluster was in the parametric stress contrast, in the lingual gyrus. B. The control contrasts. We can see that the lingual gyrus was also active here. C. The control contrast, here at z = 8. We can see that there was also some prefrontal activity in the reverse parametric effort contrast. However, this cluster was not significant when family wise error correction was performed. D. The stress-control contrast. No significant clusters were found.

E-G. The whole brain activity during the calculations. All contrasts were parametric (F and G) or reverse parametric (E) effort contrasts. For the parametric effort stress and both reverse parametric effort control and control-stress, no significant clusters of at least 50 connected significant voxels were found (p < .001). E. The reverse parametric stress contrast. No frontal activity was found in this contrast. F. The parametric control contrast. Here, activity in the medial prefrontal cortex (MPFC) and the dorsolateral prefrontal cortex (DLPFC) was found. G. The parametric effort contrast for the difference between control and stress. Here, some activity was found in the inferior frontal gyrus.

the processes of interest were investigated (i.e. DLPFC, MPFC, specifically dACC, and insula). These regions have a high anatomical precision because they were generated from the same participants. Circular inference is prevented, as we used regions based on the calculation task to analyse the data from the decision task, which is independent.

The second ROI analysis aimed at testing the effects of stress during both decision-making and calculations. For this analysis, we used an a-priori MPFC ROI based on a previous study.

Whole brain results decision-making task

The whole-brain analysis of the data from the decision-making contrasts of the effort related areas are summarized in Table 1. In this analysis, only two significant clusters were found. One in the parametric effort control contrast, and one in the parametric effort stress contrast. Figure 8 gives an overview of the activity in the parametric effort contrast during stress, control, stress-control, and

control-stress. Both of these significant clusters that were found are located within the Lingual Gyrus. No significant clusters were found in the reward related stress-control contrasts. There were two significant clusters in the high-low reward contrast. One in the Cerebellum (peak voxel: -24, -58, -20; cluster size: 242, T = 6.47, pFWE < .001) and one in the Declive (peak voxel: 28, -72, -18; cluster size: 455, T = 8.09, pFWE < .001). Contrary to what we expected, no activity was observed in dACC, MPFC, or DLPFC at the whole brain level, neither in the control, stress, or comparison contrasts.

Whole brain results calculation task

In the whole brain analysis of the calculations, the parametric effort contrast revealed significant prefrontal clusters in the control contrast as expected. A cluster in the MPFC was found (peak voxel: -4, 20, 48; cluster size: 691, T = 10.07, p_{FWE} < .001). Additionally, a cluster in the DLPFC was found (peak voxel: -44, 10, 34; cluster size: 1476, T = 7.16, p_{FWE} < .001). Furthermore, a significant insula cluster was

Table 1.

All clusters that were found during the decision-making contrasts, with a cluster size of at least 50 connected significant voxels (threshold p < .001). The reverse contrast is the contrast multiplied by -1. These contrasts were used to test for regions that become less active with higher effort. The position is reported in MNI coordinates. After applying family wise error correction (FWE), only two different clusters remained significant. One cluster was found in the parametric effort contrast during the control session, and one during the parametric effort in the stress session. Both these clusters were found in the lingual gyrus. Since we only hypothesised an effect of stress on the prefrontal regions, these clusters were not investigated further. * pFWE < .05.

Location (MNI label)	Position (x,y,z)	Cluster p-value (FWE-corr)	Peak T	Cluster size
Parametric effort control				
Fusiform gyrus	(-24,-70,-10)	0.093162	5.467724	79
Lingual gyrus	(6,-76,8)	0.00519 *	4.655265	149
	(-4,-76,12)		4.26905	
	(4,-80,16)		4.261832	
Parametric effort control reverse				
Inferior frontal gyrus	(-40,40 10)	0.315686	4.466287	52
Parametric effort stress				
Lingual gyrus	(-2,-78,-2)	<0.0001 *	7.331042	434
	(2,-82,10)		5.722619	
	(-2,-74,14)		4.915114	
Declive	(-20,-72,-12)	0.142885	4.766066	69
Posterior cingulate	(22,-66,10)	0.247702	4.748438	57

Table 2.

Locations and p-values for the ROIs that were found. The ROIs were generated using both the parametric effort and reverse parametric effort contrast in the calculation data. Here, reverse parametric effort is the parametric effort contrast multiplied by -1. Significant voxels (threshold p < .001) were clustered on proximity, and only clusters containing at least 50 neighbouring significant voxels were further analysed. The p-values for the clusters are the family wise error (FWE) corrected values. Only clusters with a FWE-corrected p-value < .05 were further analysed. Of these ROIs, only the ones that were important for our hypotheses (i.e., the medial prefrontal cortex (MPFC) and the dorsolateral prefrontal cortex (DLPFC) were investigated. In total, three ROIs were subsequently analysed. First, the superior frontal gyrus, or the MPFC. Second, the medial frontal gyrus, in this case the DLPFC, and third, the insula. We test the insula in order to find an effect of stress in the SN. * Significant cluster, with PFWE < .05; ** Significant cluster used in the ROI analysis, PFWE < .05.

Location (MNI label)	Position (x,y,z)	Cluster p-value (FWE-corr)	Peak T	Cluster size
Parametric effort				
Superior frontal gyrus	(-6,20,50)	1.02E-07 **	8.0679	394
	(-8,28,42)		4.740153	
	(4,18,44)		4.094477	
Medial frontal gyrus	(-42,24,22)	2.9E-13 **	6.94499	836
	(-48,10,38)		6.839056	
	(-52,36,14)		5.026441	
Insula	(-26,30,2)	0.039704 **	6.382373	79
	(-34,22,2)		4.14222	
Cerebellum	(32,-62,-28)	9.35E-06 *	6.323435	266
	(40,-68,-28)		6.042747	
	(32,-60,-36)		4.095436	
Declive	(-34,-74,-18)	2.99E-07 *	6.129512	362
	(-36,-86,-6)		5.387378	
	(-42,-66,-16)		5.299193	
Caudate	(-8,16,6)	0.166809	5.978674	54
Cerebellum	(8,-78,-34)	9.35E-06 *	5.484932	266
	(8,-76,-26)		5.471447	
Cuneus	(-28,-80,36)	1.72E-05 *	5.476009	250
	(-38,-84,28)		4.453924	
Inferior occipital gyrus	(30,-90,-4)	0.002058 *	5.276479	137
	(42,-86,-10)		4.609646	
	(46,-74,-14)		3.759126	
Reverse parametric effort				
Putamen	(-30,-4,2)	0.024249 *	5.775667	88
	(-30,-14,4)		3.813586	
Anterior cingulate	(-2,34,-10)	0.187573	5.698733	52
Putamen	(28,-4,0)	0.002372 *	5.254271	134
	(34,2,12)		4.722855	
	(32,6,2)		4.333956	
Inferior parietal lobe	(-58,-30,24)	0.001483 *	5.236336	144
	(-64,36,24)		4.946507	
	(-66,-34,32)		3.915671	

Anterior cingulate	(12,50,-10)	0.04694 *	5.192846	76
	(10,62,0)		4.858622	
Superior temporal gyrus	(-60,4,-2)	0.031836 *	5.142667	83
	(-56,8,-8)		4.78757	
	(-62,2,8)		4.50599	
Inferior parietal lobe	(-38,-30,44)	0.166809 *	4.896193	54
Mid temporal gyrus	(62,-40,-2)	0.176888 *	4.510745	53
	(62,-32,2)		3.762803	
Inferior parietal lobe	(62,-24,30)	0.030139 *	4.425534	84
	(64,-22,22)		4.161829	
	(56,-28,20)		3.908321	

found (peak voxel: -26, 28, 2; cluster size: 121, $T = 7.97$, $p_{FWE} = .008$). In the control-stress contrast, one prefrontal cluster was found, in the Inferior Frontal Gyrus (peak voxel: -40, 48, 0; cluster size = 83, $T = 7.57$, $p_{FWE} = .02$). A summary of these findings is given in Figure 8. We found no significant prefrontal clusters in the stress contrasts for parametric effort or reverse parametric effort. No significant clusters were found in the reverse parametric effort control contrast.

Generation of the ROIs

We then investigated the effort related regions in the calculation trials. For this analysis, we tested which clusters were significant in either the parametric effort or the reverse parametric effort contrast during the calculations. In the parametric effort contrast, a total of eight significant clusters were found (see Table 2 for a summary). In the reverse parametric effort analysis, a total of
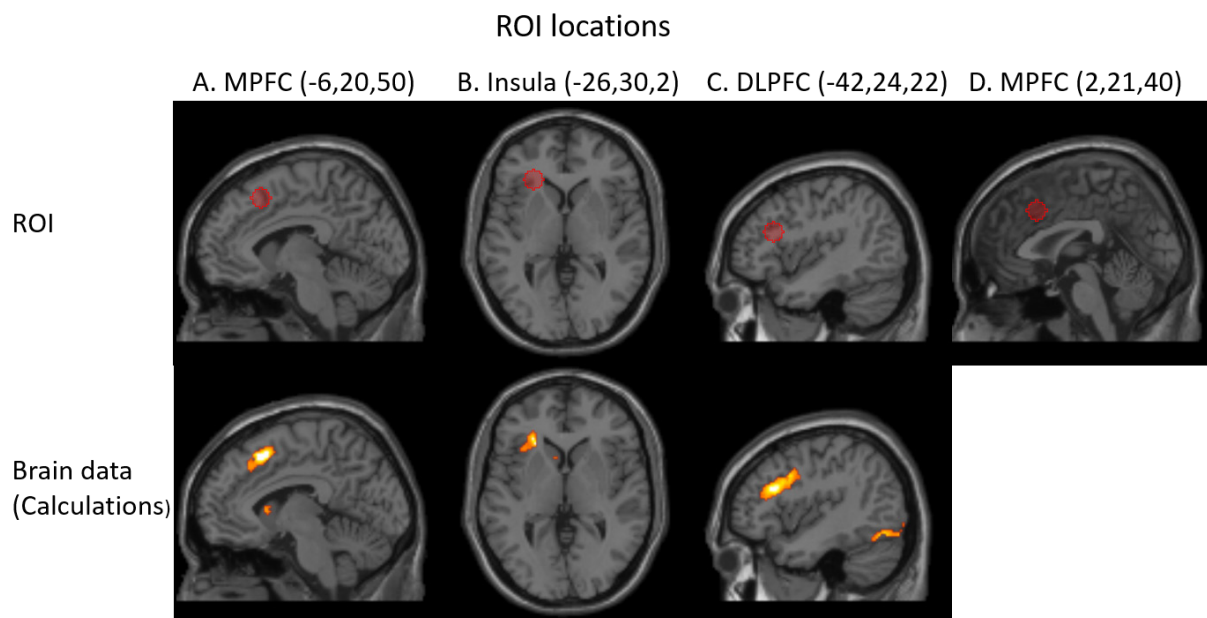
ROI locations

A. MPFC (-6,20,50)   B. Insula (-26,30,2)   C. DLPFC (-42,24,22)   D. MPFC (2,21,40)

Figure 9. The different ROIs that were generated and investigated. The top row of the figure shows the location of the ROIs that were used for the ROI analysis. The bottom row shows the corresponding activity in the calculation trials on which the ROI is based. Each ROI was defined as a sphere of 8mm around the peak voxel in the shown cluster, indicated with a red circle in this figure. The names of the regions were taken from the MNI database. **A.** The medial prefrontal cortex ROI found in the parametric effort contrast, centred on -6, 20, 50. **B.** The insula ROI found in the parametric effort contrast, centred on -26, 30, 2. **C.** The dorsolateral prefrontal cortex ROI found in the parametric effort contrast, centred on -42, 24, 22. **D.** The premade ROI centred on 2, 21, 40.

six significant clusters were found (see Table 2 for a summary).

Based on these results, we selected the clusters within the hypothesized regions for effort coding, the MPFC (including dACC) and DLPFC. We found a significant effect of both the dACC/MPFC (peak voxel: -6, 20, 50; cluster size: 394, $T = 8.07$, $p_{FWE} < .001$, Fig. 9A) and the DLPFC (peak voxel: 42, 24, 22; cluster size: 836, $T = 6.95$, $p_{FWE} < .001$, Fig. 9C) in the parametric effort contrast. Furthermore, to study the effect of stress in the SN, a preliminary analysis to the insula region was conducted. This region was found significant in the parametric effort contrast as well (peak voxel: -26, 30, 2; cluster size: 79, $T = 6.38$, $p_{FWE} < .04$, Fig. 9B).

MPFC ROI

When investigating the Superior Frontal Gyrus, a significant effect of reward ($F(1,21) = 5.94$, partial $\eta^2 = 0.22$, $p = .02$, Fig. 10A) was found, indicating higher activity in low reward trials compared to high reward trials. The significant effort x reward interaction ($F(3,63) = 3.12$, partial $\eta2 = 0.13$, $p = .03$, Fig. 10B) revealed that this effect was mainly present in the lower effort trials (very easy and easy). Furthermore, a significant main effect of block was found ($F(1,21) = 7.91$, partial $\eta2 = 0.27$, $p = .01$), indicating higher signal change in the first block compared to the second block. An order x type x effort x reward interaction was found ($F(3,63) = 4.35$, partial $\eta2 = 0.17$, $p = .008$). However, no significant effects of stress on reward were found in the follow-up test after multiple comparison correction. Additionally, no effect of stress on effort was found (control first, low reward: $F(3,33) = 2.66$, partial $\eta2 = 0.20$, $p = .06$; control first, high reward: $F(3,33) = 0.87$, partial $\eta2 = 0.07$, $p = .47$, stress first, low reward: $F(3,30) = 0.97$, partial $\eta2 < 0.01$, $p = .42$, stress first, high reward: $F(3,30) = 0.80$, partial $\eta2 = 0.07$, $p = .51$).

DLPFC ROI

This analysis revealed a significant interaction effect of type x effort x reward ($F(3,63) = 4.60$, partial $\eta^2 = 0.18$, $p = .006$). The follow-up tests found no significant effect of stress on reward coding after multiple comparison correction.

Separate ANOVAs testing for stress effects on effort coding for each reward separately did not find a significant difference (low reward: $F(3,66) = 2.69$, partial $\eta^2 = 0.11$, $p = .05$, high reward: $F(3,66) = 1.97$, partial $\eta^2 = 0.08$, $p = .13$). Additionally, a significant effect was found in the session order x type x effort x reward interaction ($F(3,63) = 3.62$, partial $\eta^2 = 0.15$, $p = .02$). In the control first, very hard effort condition, a significant effect of type x reward was found ($F(1,11) = 21.45$, partial $\eta^2 = 0.66$, $p = .001$, Fig. 10C). Post-hoc t-tests confirmed lower activity in the high reward trials compared to low reward trials in stress ($T(11) = 4.77$, partial $\eta^2 = 0.71$, $p < 001$), but not in control ($T(11) = -1.36$, partial $\eta^2 = -0.40$, $p = .20$). Testing the effect of stress on effort only revealed a significant interaction in the control first, high reward condition, before correction for multiple comparisons (control first, low reward: $F(3,33) = 2.12$, partial $\eta^2 = 0.16$, $p = .12$; control first, high reward: $F(3,33) = 4.84$, partial $\eta^2 = 0.31$, $p = .007$, stress first, low reward: $F(3,30) = 0.59$, partial $\eta^2 = 0.06$, $p = .62$, stress first, high reward: $F(3,30) = 0.55$, partial $\eta^2 = 0.05$, $p = .65$, Fig. 10D).

Additionally, there was a significant order x type x block interaction ($F(1,21) = 4.88$, partial $\eta^2 = 0.19$, $p = .04$), indicating that only in the stress first condition, the activity decreased after the first block in the stress condition ($T(22) = 2.98$, partial $\eta^2 = 1.05$, $p = .01$, Fig. 10E). This was not the case in the control condition ($T(22) = 1.52$, partial $\eta^2 = 0.34$, $p = .16$). This indicated a decreased executive control network after stress.

Insula ROI

The ROI in the insula was tested in order to study the effect of stress in the SN. Here, we found a type x block interaction in the ANOVA ($F(1,21) = 4.71$, partial $\eta^2 = 0.18$, $p = .04$, Fig. 10F), yielding a trend for decrease in activity in the control condition in block two ($T(22) = -2.03$, partial $\eta^2 = -0.55$, $p = .06$), while it remained elevated in the stress condition ($T(22) = 0.11$, partial $\eta^2 = 0.03$, $p = .91$). Given that the insula is part of the salience network, this indicates elevated activity in the salience network after stress, which is in line with previous studies (Hermans et al. 2014). No other significant effects were found in this ROI.
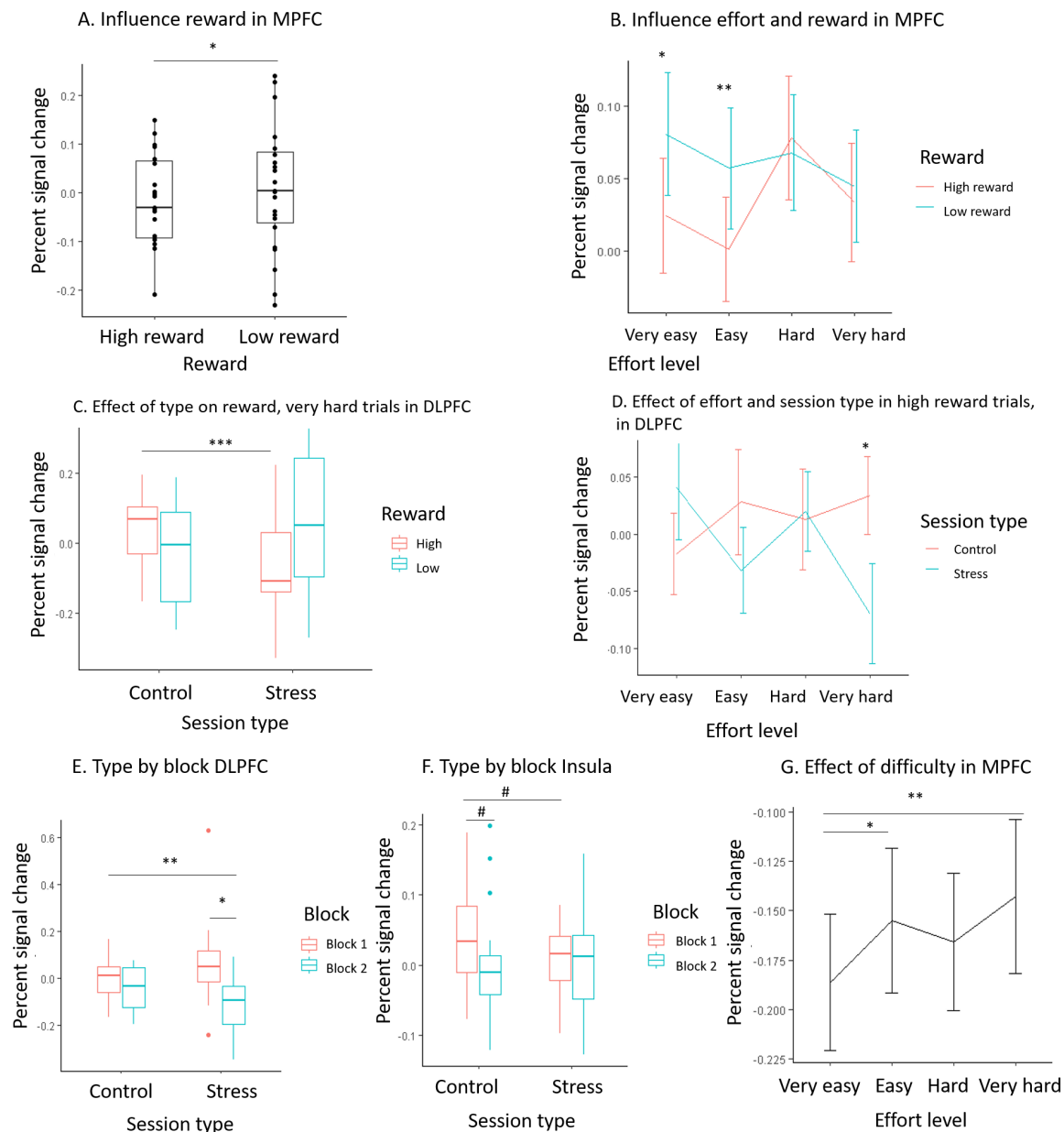
Figure 10. Effects found in the ROI analysis. A. Influence of reward on percent signal change in the medial prefrontal cortex (location -6,20,50). In the low reward condition, a significantly higher percent signal change was found compared to the high reward. B. Splitting this effect by effort level shows that this effect was driven by a significant difference in the very easy and easy effort levels. C. The effect of session type and reward on percent signal change in the dorsolateral prefrontal cortex (location -42, 24, 22), including only very hard trials. A significant effect of session type was found in high reward, but not in low reward. D. Effect of effort and session type on percent signal change in high reward trials. A significantly lower percent signal change was found in the very hard stress trials when compared to very hard control trials. Additionally, the slopes differ significantly, giving a significantly lower slope of the percent signal change with effort interaction in stress, compared to control. E. The influence of session type and block in the dorsolateral prefrontal cortex (location -42, 24, 22) in the stress first condition. There was a significant decrease of percent signal change in block 2 of the stress session, but not in the control session. F. The influence of type and block in the insula (location: -26, 30, 2). There was a trend for a decrease in percent signal change in block two of the control session compared to block one of the control session. G. Influence of effort on the independently generated ROI (location: 2, 21, 40). Percent signal change can be seen increasing as a function of difficulty level. This effect was significantly different between the very easy and easy trials, as well as the very easy and very hard trials. # p < .1, * p < .05, ** p < .01, *** p < .001.

Independent ROI analysis: MPFC

The independent ROI analysis investigating MPFC activity in the decision phase data revealed a higher percent signal change in block one compared to block two ($F(1,21) = 11.02$, partial $\eta^2 = 0.34$, $p = .003$). Furthermore, an order x type x effort x reward interaction was found ($F(3,63) = 3.86$, partial $\eta^2 = 0.16$, $p = .01$). The follow-up analysis found no significant effect stress on reward coding in control or stress first after multiple comparison correction. No significant effects of stress on effort coding were found (control first, low reward: $F(3,33) = 2.74$, partial $\eta^2 = 0.20$, $p = .06$, control first, high reward: $F(3,33) = 0.51$, partial $\eta^2 = 0.04$, $p = .68$, stress first, low reward: $F(3,30) = 0.29$, partial $\eta2 = 0.03$, $p = .84$, stress first, high reward: $F(3,30) = 1.15$, partial $\eta^2 = 0.10$, $p = .35$). No effect of stress was found in this analysis.

The independent ROI analysis in the calculation phase only found a significant main effect of effort ($F(3,60) = 4.07$, partial $\eta^2 = 0.17$, $p = .01$, Fig. 10G), indicating that activity increased as a function of effort. No significant effect of stress was found in this analysis.

Discussion

This study investigated the effects of stress on effort-based decision-making. We combined an already established effort-based decision-making task with experimental induction of acute stress in a within-subject design. As hypothesized, the results showed that acute stress reduced participants' willingness to engage in mental effort. Further, participants performed better and faster in the calculations when they had a higher tension score. At the neural level, effort activated the MPFC (specifically, the dACC) and the DLPFC in the control condition during calculations. However, no effect of stress or effort coding was found on these regions during the decision making task. The ROI analysis revealed some evidence for reward and effort coding in the dACC, but no main effect of stress. The DLPFC exhibited some sensitivity to effort and reward, but only in a complex interaction with stress and session order. Finally, the pupil analysis revealed an effect of stress during the calculation trials. These results have important implications for understanding the effects of stress on decision-making, with relevance for stress-related disorders with motivational deficits.

Promised reward and expected effort influence the decisions to engage in a task. This was experimentally established in previous research, showing that easier and more rewarded options are accepted more (Kool et al., 2010; Shenhav et al., 2017). As expected, this experiment confirmed this effect of effort and reward; participants accepted harder trials less often, and higher reward trials more often. We found that stress reduced the willingness to engage in mental effort, as expected. Previous research also provided some indication that stress might influence effort-based decision-making. Activity in similar brain areas was found during both acute stress and decision-making (Silvetti et al., 2018; Valentino & Bockstaele, 2008; Gathmann et al., 2014). Effects of stress on other forms of decision-making have consistently been reported. For example, people under stress were found to become more risk-taking and were more likely to exhibit habitual over goal directed behaviour. (Schwabe & Wolf, 2009; Starcke & Brand, 2012; Starcke & Brand, 2018). Interestingly, chronic stress in rats was shown to increase reward insensitivity through VTA activation (Tye et al., 2012; Hollon et al., 2015) and acute stress in rats resulted in effort avoidance (Shafiei, Gray, Viau, & Floresco, 2012). However, differences might arise because these are animal studies, rather than studies in humans. Furthermore animal studies also showed that different forms of stress can cause different reactions in DA neurons (Valenti & Grace, 2012).

Considering the effects of stress on behaviour, our main behavioural results confirmed that experimentally induced acute stress reduced the willingness to engage in mental effort, making people more effort avoidant. Furthermore, we found a trending effect of stress on the interaction of effort and reward, seemingly decreasing the acceptance rate in high reward, high effort trials, as well as low reward, low effort trials. This result might be interpreted as evidence for both effort avoidance and reward insensitivity. However, we should be careful with this interpretation, as this effect was not significant.

Previous work also shows that higher effort avoidance was observed in patients suffering from depression (Bishop & Gagne, 2018; Treadway, Bossaller, Shelton & Zald, 2012), while patients suffering from anxiety show an increased willingness to exert effort (Bishop & Gagne, 2018). The results of our covariate analysis are in line with the latter: a higher tension score, also called anxiety in the POMS, led to higher acceptance rates. However, no effect of depression on acceptance rate was found. This might be because the study was performed on only a part of the original sample, causing lack of power. Additionally, we found that participants which perform better at the training task accepted significantly more trials, and performed the calculations in the scanner faster and more accurate, as expected. This highlights the importance of taking individual differences in performance into account.

Studies have shown that heart rate increases with stress (Shapiro et al., 2000; Rieger, Stoll, Kreuzfeld, Behrens, & Weippert, 2013). Heart rate variability was found to decrease during (Shapiro et al., 2000) and after (Rieger et al., 2013) stress. In our study, we used the IBI (the inverse of the heart rate), and RMSSD to test whether the stress induction was performed successfully. Unexpectedly, we found that the heart rate did not differ significantly between the stress condition and the control condition. The RMSSD did not show a significant decrease under stress, although a trend for this decrease was observed. The lack of significance could have a few reasons. As mentioned before, the analysis was run on an incomplete sample. Besides this, an effect of session order was found in the RMSSD analysis, where the participants that had the stress session first had an overall lower RMSSD score. This indicates that there might have been a difference in experienced stress in the stress first compared to the control first session. Specifically, as a lower RMSSD has been found in the stress first condition, the participants that started with the stress session might have experienced more stress overall. This might further decrease the power of this analysis.

When testing the effect of IBI during the calculations and decisions, we found that during the calculations, an increase in IBI (lower heart rate) correlated with a better performance. This is in line with previous work which shows that stress negatively impacts both motivation and working memory (Roozendaal et al. 2004; Schwabe et al. 2012), and therefore decreases performance. During the decision-making task, we found that in the very hard trials, a lower IBI – and thus presumably higher stress – caused reward insensitivity (reduced acceptance of high reward trials, and more acceptance of low reward trials). This indicates that the beneficial impact of reward on very hard trials was neutralized under stress. This partly confirmed our hypothesis that stress causes reward indifference, however, only for the very hard trials. That this effect was only found in the very hard condition was unexpected.

Furthermore, we attempted to test the impact of all covariates in a single full model, to determine the relative weight (including heart rate, training accuracy, the tension subscale of the POMS, and the depression subscale of the POMS). However, in all cases (except for the acceptance ratio model), this model did not converge. This issue could be caused by having a model that is too complex for the amount of data.

Research into neural effects of stress found that the regions activated by stress and effort-based decision-making partially overlap (Silvetti et al., 2018; Valentino & Bockstaele, 2008; Gathmann et al., 2014). For example, the dACC, DLPFC and MPFC were found to be part of both the stress and the effort-based decision-making response. Our findings in the whole brain analysis during the decision-making task unexpectedly did not support these findings; no significant effect of stress on effort-based decision-making in prefrontal regions was found. Our findings in the whole brain analysis of the calculations found activity in both the DLPFC and MPFC regions in the parametric effort contrast, but only in the control sessions. This activity was no longer significant in the stress or stress-control contrasts. This provided some indication that DLPFC and MPFC activity during effortful calculations was reduced under stress. However, this did not survive direct comparison, possibly due to lack of power (small sample size). An additional caveat concerns the level of the experienced stress during the experiment. Although we

did find a successful stress induction – there was an effect of stress on heart rate and behaviour – the participants might have experienced more stress overall when they started with the stress session, as indicated by the RMSSD analysis. These session order effects may thus further reduce power.

The results of the ROI analysis are partly in line with the literature findings that MPFC and DLPFC are implicated in both effort-based decision-making and stress (Gathmann et al., 2014). In our analysis, we found an effect of reward on the MPFC, and an interaction between reward and effort, which is in line with this literature. We found a higher MPFC activity for less reward. This could be explained by the participants assuming that the high reward is the baseline reward they can get. This would coincide with the literature, where a higher activity for reduced reward compared to baseline reward has been found in a region partly overlapping with our ROI (Bush et al., 2001). In the DLPFC, we could not find a main effect of effort or reward. Unexpectedly, we could not confirm a main effect of stress on either the MPFC or the DLPFC. We did find that stress had an effect on reward coding in the DLPFC, but only in the participants that started with the control session, and only in very high difficulty trials. We also found that stress had an effect on effort coding in the DLPFC in these participants, but only in the high reward trials. There could be multiple reasons as to why we do not find these results in the other conditions or the MPFC. First, our sample size was not sufficiently large. Second, the session order might have influenced the stress experience of the participants. Our RMSSD analysis revealed an overall decrease in RMSSD in the participants that started with the stress session. Since a decrease in RMSSD would be expected under stress (Shapiro et al., 2000), this indicated that having the stress session as first session might have induced stress in itself, also in the control condition.

The results of the a-priori ROI analysis show no main effect of effort, reward or stress on the decision-making analysis. An effect of effort was found in the calculation analysis. The fact that differences have been found with the analysis of the MPFC in the decision-making trials, could be due to the ROI we generated having a higher anatomical precision than the a-priori ROI, because we created this ROI based on the regions that were active in the sample of participants we tested. However, it was unexpected that we did not find an effect of stress in neither regions.

Previous studies on pupil size found an increase in pupil size with increasing mental effort (Hess & Polt, 1964; see van der Wel & van Steenbergen, 2018, for a review). Moreover, pupil size has been correlated with sympathetic nervous system activation, and used as a marker for stress in the literature (Bali & Jaggi, 2015). Both NA and DA were increased during stress (Hermans et al., 2014). Animal studies also found increased NA and DA in decision making (Salamone et al., 2018; Varazzani et al. 2015). Furthermore, stress is reported to increase NA produced by the LC (Ironside et al., 2018), which was found to positively correlate with pupil size (Murphy et al. 2014). This line of work thus suggests that stress should increase pupil size. Our study did find an increase in pupil size with increased effort, suggesting that pupil size is indicative of task difficulty, or possibly the amount of mental effort participants invest in the task (Silvestrini & Gendolla, 2019), as expected. Since the pupil size is a putative measure for NA, this might be seen as evidence for part of the RML: the LC module modulates the amount of effort (Silvetti et al. 2018). Unexpectedly, no significant effect of stress on pupil size was found, during neither calculations nor decisions. However, this might be due to not having a sufficiently large sample size, and by the possible effect of session order on stress.

Concluding, this thesis found evidence for the hypothesis that effort-based decision-making was influenced by stress at the behavioural level. However, the hypothesized underlying neural dynamics were not observed. A neural effect of stress on effort was found only in the MPFC of the participants that started with the control session, and only in the high reward condition. A neural effect of stress on reward was only observed in the MPFC of the participants that received the control session first, in the very hard trials. Effort was tracked by pupil size, but only during the calculations. Furthermore, no evidence was found for the hypothesis that pupil changes tracked the impact of

stress. However, due to the small sample size of the study, these effects might not be found due to a problem with the power of the study. Therefore, the results of the analysis of the complete sample of the study might give more conclusive evidence to whether these hypotheses are true.

As discussed before, this study has some limitations. First of all, due to the Covid-19 pandemic, the full sample has not been tested yet. Therefore, the power in this study might be lacking, and more reliable results will be found when the entire sample has been tested. Secondly, individual differences in the experienced difficulty of the calculations have been observed through different overall accuracies for different participants. This might lead to a different expected value for different participants, since the probability to respond correctly to a certain difficulty may vary. Ignoring this might lead to a reduction in power. Additionally, the models used for the behavioural analysis often experienced some errors due to the complexity of the models. Finally, evidence for an effect of session order was found, potentially reducing the observed effect of stress.

Future research may test the activity of the VTA and LC during both stress and effort-based decision-making, as it has been shown that both the VTA and LC play an important role in the effects of stress and motivation (Hollon et al., 2015, Tye et al., 2012, Valentio & Bockstaele, 2008), and they are vital parts of the proposed RML model (Silvetti et al., 2018). This research might be conducted by analysing the data from the GRE and TSE scans made, and could elucidate the role of the VTA and LC during stress. Another direction for further research is to complete the full sample of this study. Due to the Covid-19 pandemic, the sample was not fully tested. This would give an increase in power that might have consequences for the results found in this research. Another possibility for improvement would be using more advanced modelling techniques to redefine the effort levels in such a way that they are similar for all individual participants. Then, the power of the analysis could be increased. Finally, further research might involve testing the reinforcement meta-learner model on these data, once it is expanded to include the functional data from the VTA and LC, to

investigate what the influences of stress are on the model parameters of the RML model.

The results of the study of the complete sample could further help unravel the interaction between stress and effort-based decision-making. It might furthermore be important in giving a clearer understanding of the working mechanisms of stress-related disorders, especially those where motivation plays a role, like burnout and PTSD.

Acknowledgements

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