



Cortisol modulates the engagement of multiple memory systems: Exploration of a common *NR3C2* polymorphism

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ABSTRACT

Exposure to acute stress has been shown to result in a shift from declarative toward non-declarative learning, presumably mediated by brain mineralocorticoid receptors (MRs). In this study, we aimed to replicate and extend these findings by investigating the role of stress-associated cortisol secretion on learning behavior. Furthermore, we explored the influence of a well-characterized common single nucleotide polymorphism of the MR gene (rs2070951; minor allele frequency: 49.3%) previously shown to influence MR expression and HPA axis activity. Healthy males ($n = 74$) were exposed to the Trier Social Stress Test or a control condition prior to performing a probabilistic classification task (Weather Prediction Task). The use of a non-declarative learning strategy continuously increased over the course of the learning task after stress exposure, but leveled in the control condition. The shift toward a non-declarative strategy in the stress group was associated with better learning performance. Higher pre-stress cortisol levels favored the adoption of a non-declarative learning strategy. rs2070951 C/C-carriers in contrast to G-allele carriers exhibited a larger secretion of cortisol under stress. Furthermore, control participants homozygous for the C-allele adopted a non-declarative learning strategy less often than stressed participants, whereas the choice of strategy was independent of stress in G-allele carriers. The failure to switch strategies resulted in poorer performance, suggesting a beneficial effect of stress in dependence of MR variation. Consistent with previous findings, the results provide further support for cortisol as a driving force in coordinating the competition between multiple memory systems under stress.

1. Introduction

Instrumental learning is thought to be under the control of a hippocampal declarative and a striatal non-declarative system, which interact with each other (Poldrack et al., 2001). An important question is what factors determine which of the systems is engaged to guide behavior. It is well documented that stress affects cognition (McEwen and Sapolsky, 1995), mediated through corticosteroid action on brain mineralocorticoid receptors (MRs) as well as glucocorticoid receptors (GRs) (de Kloet et al., 1990). A growing body of work has demonstrated an influence of acute stress on the function of multiple memory systems (Fournier et al., 2017; Goldfarb et al., 2017; Schwabe and Wolf, 2013; Wirz et al., 2018). In particular, several studies describe a stress-induced shift from a flexible, cognitively demanding, declarative learning system in favor of rigid, undemanding habits driven by the non-declarative memory system (Fournier et al., 2017; Schwabe et al., 2009; Schwabe and Wolf, 2012a) which might rescue learning performance under stress (Schwabe et al., 2013). fMRI-data support the latter

finding by illustrating that striatal activity during instrumental learning is more pronounced in stressed participants at the expense of hippocampal activity (Schwabe and Wolf, 2012a), which seems to be orchestrated by the amygdala (Packard and Wingard, 2004; Schwabe and Wolf, 2012a; Vogel et al., 2015). Recently, two studies reported that the shift in the dominant memory system depends on stress-induced hypothalamic-pituitary-adrenal (HPA) axis reactivity (Smeets et al., 2018; Vogel et al., 2017). Taken together stress leads to the preference of a habitual, non-declarative memory system whilst inhibiting explicit declarative learning in an adaptive manner. There is evidence to suggest that the MR has a critical role in orchestrating the switch between multiple memory systems (Schwabe et al., 2009, 2013; Vogel et al., 2016; Wirz et al., 2018). Brain MRs are located in the cytoplasm as well as in cell membranes. Membrane-bound MRs induce rapid, non-genomic effects, whereas cytoplasmatic MRs induce slow, genomic effects affecting gene transcription and translation (Joëls et al., 2012; Vogel et al., 2016). MRs are found to be expressed at extra-nuclear sites including presynaptic terminals, neuronal dendrites,

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dendritic spines and post-synaptic membrane densities of excitatory synapses (Prager et al., 2010). Interestingly, corticosteroid activation of membrane-bound MR was discovered to quickly induce an enhancement of glutamate transmission in hippocampal area (Karst et al., 2005) as well as in the basolateral amygdala (Karst et al., 2010). Schwabe et al. (2013) demonstrated that a pharmacological blockade of the MR prevents the stress-induced switch to the striatum-based non-declarative memory system, which was associated with a reduction in learning performance under stress. The latter may be attributed to an inhibition of amygdala-striatum connectivity through MR blockade (Vogel et al., 2015). Collectively, recent research supports the notion of an adaptive organization of memory systems by stress via a cortisol-induced activation of the MR. Given its critical role in orchestrating these processes, the investigation of genetic variation of the MR might thus help to understand interindividual variability in stress-associated memory function. Several studies have reported a relationship between different MR single nucleotide polymorphisms (SNP) and alterations in HPA axis activity (DeRijk and de Kloet, 2008; Li-Tempel et al., 2016; Taylor et al., 2014; van Leeuwen et al., 2010, 2011). The C-allele of one well-characterized MR polymorphism (rs2070951) is associated with an increased expression and transactivation capacity of the MR in vitro (DeRijk et al., 2006) as well as with an enhanced HPA axis reactivity (DeRijk, 2009; van Leeuwen et al., 2010, 2011). Interestingly, a recent study of (Wirz et al., 2017a) provide evidence for a link between CA-carriers of haplotype 2 (MR-2 G/C C, MR-I 180 V A) and the stress-induced shift towards the non-declarative memory system. The present study aimed to replicate and extend findings on the effects of stress on engagement of multiple memory systems in the context of a probabilistic classification learning task. We sought to investigate the association between stress-induced cortisol levels and choice of learning strategy as well as learning performance. Furthermore, we explored the association between genetic variation of the MR and choice of learning strategy as well as performance in the learning task.

2. Materials and methods

2.1. Participants and design

The sample consisted of 74 healthy men with a mean age of 24.38 years (range: 18–34; SD = 4.24) and a Body Mass Index in the range of 18.8–29.9 (Mean = 23.61; SD = 2.63) who were recruited by online advertisements in social media networks, mailing lists and advertisements on notice boards throughout the Ruhr University Bochum and surrounding Universities. Participants were randomly assigned to the stress and control group, which did not differ in age ($t(73) = -.641$, $p = .524$) or BMI ($t(73) = -.844$, $p = .401$). Participation was limited to those, without medication intake and with no reported history of any psychiatric or neurological disorder. In view of well-established effects of smoking and excess of weight on acute stress reactivity (Rohleder and Kirschbaum, 2006; Rotenstein et al., 2015), only non-smokers with a BMI between 18 and 30 were included in the present study. Given that (Wirz et al., 2017a) showed that only male CA haplotype (MR-2 G/C C, MR-I 180 V A) carriers exhibited an enhanced use of non-declarative strategies after stress and with respect to a reduction of complexity, we focused on male participants only. To control for diurnal rhythm of cortisol, all testing took place in the afternoon (between 12.30 a.m. and 6.30 p.m.). All participants provided written informed consent in accordance with procedures approved by the local ethics committee at the Ruhr University Bochum and were financially compensated with 12 Euro. In order to examine the effects of the MR polymorphism on stress-induced changes in the engagement of multiple memory systems and learning performance, we used a 2×2 between-subject design with the factors stress (TSST vs. control) and genetic variant of the focused MR-2 G/C (C/C-carriers vs. G-carriers).

2.2. Experimental procedure

Participants received an e-mail a few days before the experiment, which asked them to refrain from caffeine, nicotine, food and any drinks except for water 2h before the experimental session. Furthermore, we asked them to refrain from sports, drugs and alcohol 24h before the start of the experiment. After arrival, the participants rested for 15 min during which time they read study information, which contained information about the treatment (stress / control), gave written consent and provided a salivary sample for DNA extraction via mouthwash. Thereafter each participant provided his first saliva sample (baseline) and completed a short questionnaire about his emotional state (Subjective Emotional Response Scale; SERS). Next, the participant underwent the treatment (stress / control condition). Afterwards he provided the second cortisol sample (+2) and answered subjective stress ratings. Before the third cortisol sample (+10), the investigator explained the Weather Prediction Task (WPT) to the participant. Subsequent to the salivary sample, the participant started the WPT. This interval between stress and learning task was chosen because of the slow reaction of the HPA axis, which leads to peak levels of the stress hormone cortisol at about 25 min after stressor onset (Dickerson and Kemeny, 2004). Directly after the WPT the fourth salivette was given to the participants (+20). Participants then completed questionnaires (demographic data, PHQ-9). The fifth sample (+45) was obtained to measure the stress-recovery. Finally, the participants were debriefed and paid their monetary compensation.

2.3. Stress and control manipulation

Participants in the stress condition underwent the Trier Social Stress Test (TSST), which is a reliable method to increase the activity of the autonomous nervous system (ANS) as well as the HPA axis. Subsequent to 3 min of preparation, each participant was asked to give a 5-minute free speech in front of a panel (1 male/ 1 female). Afterwards the participant had to solve a mental-arithmetic task by counting backwards from 2023 in steps of 17 (for details see Kirschbaum et al., 1993). In the control condition, participants watched a 15-minute documentary (nature) film without any stress eliciting factors. To assess the effectiveness of the stress induction, salivary cortisol and emotional response were measured at several time points across the experiment. Saliva samples were collected with Salivette® (Sarstedt AG Nümbrecht, Germany) collection devices at several time points (see above). Saliva samples were stored at -20°C until analysis. Free cortisol concentrations were measured using an enzyme-immunoassay (ELISA; Demeditec Diagnostics GmbH, Kiel, Germany). Salivary cortisol determination of three samples was unsuccessful. The emotional response to treatment was evaluated using the Subjective Emotional Response Scale (SERS; factors: *arousal*, *self-directed emotions* and *anxiety*) in parallel to each salivary sample (Schwaiger et al., 2016). A total *emotional stress* score was calculated by sum of all factor values.

2.4. Probabilistic classification learning task

The „weather prediction task“ (WPT) is a probabilistic classification learning task and is frequently used to investigate neuronal as well as behavioral correlates of multiple memory systems (for more details see Gluck et al., 2002; Knowlton et al., 1996, 1994; Poldrack et al., 2001). Participants learn how to predict ‘sun’ and ‘rain’ with the help of different cards based on trial-by-trial feedback. Between one and three (out of four) cards appeared on each trial, yielding 14 different cue patterns. These cue patterns were associated with two possible outcomes (sun and rain) in a probabilistic manner. The used probabilities were same as in previous studies using this task (Gluck et al., 2002; Knowlton et al., 1994, 1996; Schwabe et al., 2013; Schwabe and Wolf, 2012a). A response was counted as correct if it matched the outcome with the highest probability for that cue pattern. Participants completed

200 trials (4 blocks with 50 trials each). On each trial, they saw 1 of the 14 cue patterns and had max. 2000 ms to respond by pressing one of two buttons with the right hand that corresponded with the outcomes 'sun' and 'rain'. After a short delay of 500 ms they received feedback (2000 ms) by presenting a happy or a sad smiley and a picture of 'sun' or 'rainy cloud'. After each block of 50 trials, participants were given the possibility to have a short break of 3 min maximum.

Assessment of learning strategies. The used learning strategy was classified with a mathematical model in which the actual response of a participant across each block and across the whole task were compared with ideal responses if a participant was reliably using a particular strategy (for details see [Gluck et al., 2002](#)). We constructed perfect response patterns that were expected across 200 trials if a participant was consistently using a specific strategy. A least-means-squared estimate resulted in a fit-value ranging from 0 to 1 indicating the fit between the ideal data for each strategy and the participants actual response (0 = perfect fit). Participants were assigned the strategy with the best-fit score for each block as well as overall. In line with previous studies (e.g. [Schwabe et al., 2013](#); [Schwabe and Wolf, 2012a](#); [Wirz et al., 2017a](#)), we divided the three strategies that participants may use to solve the probabilistic classification learning (PCL) task (Single-cue, Singleton and Multi-cue) into „simple“ (including Single-cue and Singleton) and „complex“ (including Multi-cue) strategies. Referring to [Rustemeier et al. \(2013\)](#) we called participants who used a simple strategy „declarative learner“ (DL), whereas those who used a complex strategy were classified as „non-declarative learner“ (NDL). Participants with a best-fit score smaller than 0.1 and those with a random response pattern (i.e. nearly 50-50 likelihood of 'sun' or 'rain' ([Meeter et al., 2006](#))) were classified as 'non-learners' (n = 12).

Although dichotomization may involve a loss of information, a categorical classification (DL vs. NDL) allows investigating stress-induced differences in the predominant memory system ([Wirz et al., 2017a, 2017b](#)) and ensures a better comparability with previous studies using the weather prediction task (e.g. [Schwabe and Wolf, 2013, 2012a](#); [Wirz et al., 2017a](#)).

2.5. DNA extraction and genotyping

Participants were genotyped for one single nucleotide polymorphism (SNP) of the MR gene (*NR3C2*; rs2070951 [MR-2 G/C]). This polymorphism is a functional SNP located 2 nucleotides before the translation site of exon 2 of the MR gene (minor allele frequency: 49.3%; [DeRijk, 2009](#); [van Leeuwen et al., 2011](#)). The MR-2 G/C SNP is located outside the MR coding region but inside a Kozac translation regulatory sequence which regulates MR transcription ([Ter Heegde et al., 2015](#)). For genetic analysis, DNA was extracted from a salivary sample obtained via mouthwash using 10 ml of Listerine. Salivary samples were stored at +8 °C until analysis. DNA was isolated from saliva using the MasterPure™ DNA Purification Kit (Epicentre, Biotechnologies, USA). Genotyping of the MR polymorphism was performed subsequent to the amplification of the fragment by polymerase-chain-reaction (PCR) via high-resolution melt analysis (HRM). For this SNP we used specific, best-fitting primers (rs2070951; forward: agaatatgtttgtgcttagca, reverse: GTGGTAGCCTTTGGTCTCCA), which generated a fragment of 123 base pairs. Since the C-allele of rs2070951 seems to be related to higher MR transactivation and expression (e.g. [DeRijk et al., 2006](#)) as well as an enhanced HPA-axis activity (e.g. [van Leeuwen et al., 2011](#)), C/C-carriers were treated as one group and were tested against G-carriers (C/G; G/G). See Supplemental information for results of the genotypic model (C/C vs C/G vs G/G).

2.6. Statistical analysis

All statistical analysis were performed in IBM SPSS Statistics 20 (Armonk, USA) for Windows with the alpha level of significance set to $\alpha = .05$ for all analyses (two-tailed). Before conducting the analysis,

dependent variables were tested for the assumptions of normality (Kolmogorov-Smirnov-test) and homogeneity of variance (Levene-test). If violations of the latter assumptions were observed ($p < .05$), log-transformations were disposed or non-parametric tests applied (Chi-square test, Cochran's Q test). We used Greenhouse-Geisser correction to adjust violations of sphericity (corrected dfs reported). In case of significant or trend-significant interactions, we conducted appropriate post-hoc tests. η^2 values are given as an effect size measure. Subjective stress ratings and cortisol data were analyzed using 2 (stress: TSST vs. control) x 5 (time: tbaseline,t+2,t+10,t+20,t+45) mixed-design analyses of variance (ANOVAs) with the latter factor being a repeated measure. Differences in overall learning strategy in dependence of treatment were examined by Chi-square tests. In order to investigate differences in changes of the used learning strategy over the course of the learning task, we conducted Cochran's Q-tests. Subsequently, we excluded 12 participants who were assigned to the random strategy from further analysis if learning strategy as a factor was relevant. To further examine differences in learning performance in dependence of treatment and learning strategy, we conducted a 2 (stress: TSST vs. control) x 2 (learning strategy: DL vs. NDL) x 4 (time: 4 blocks of 50 trials) mixed ANOVA with time as a repeated measure. Since block 4 is assumed to be the best indicator of a participant's ultimate strategy ([Gluck et al., 2002](#)), we also analyzed differences in learning performance with respect to block 4 via 2 (stress: TSST vs. control) x 2 (learning strategy: DL vs. NDL) univariate ANOVA. In order to analyze a possible determination of learning strategy by stress we used binary logistic regressions. Additionally, we explored the relationship between variants of rs2070951 and learning strategy in dependence of stress via chi-square tests. We performed a 2 (rs2070951: C/C vs. C/G & G/G) x 2 (stress: TSST vs. control) x 4 (time: 4 blocks of 50 trials) mixed ANOVA to reveal differences in learning performance between MR gene variants in dependence of treatment. The influence of genetic variants on stress reactivity were examined via 2 (rs2070951: C/C vs. C/G & G/G) x 2 (stress: TSST vs. control) x 5 (time: tbaseline,t+2,t+10,t+20,t+45) mixed ANOVAs with cortisol as well as subjective stress ratings as dependent variables.

3. Results

3.1. Subjective and physiological response to stress

Fig. 1 depicts cortisol responses (panel A) and emotional stress (panel B) for the control and stress group, showing successful stress induction through the TSST. There was a significant increase in cortisol concentration subsequent to the TSST but not in the control condition (time x treatment: $F(2.26,255.6) = 31.97$, $p < .001$, $\eta^2 = .317$). Peak cortisol levels were reached 25 min after the onset of the stressor (t + 10), when behavioral testing started. Subjective stress ratings also significantly increased after exposure to the TSST in contrast to control condition (time x treatment: $F(2.27,158.54) = 34.81$; $p < .001$, $\eta^2 = .332$). Post-hoc comparison showed that 2 min ($t(47.78) = -7.27$; $p < .001$) and 10 min after treatment ($t(66.10) = -2.95$; $p = .004$), emotional response to the TSST was significantly higher compared to control condition.

3.2. Treatment effects on multiple memory systems

Overall, there were no differences in learning strategy between the stress and the control group ($\chi^2(1,74) = .522$, $p = .470$). Analysis of changes in learning strategy over time showed that the number of participants using non-declarative learning strategy increased over the course of the experiment (Cochran's Q-Test; $Q(3,74) = 23.89$, $p < .001$), with the stress group showing a continuous increase over the four blocks ($Q(3,37) = 14.00$, $p = .003$). In contrast, the control group remained stable after the initial increase from block 1 to block 2. With regard to learning performance, a significant main effect of time

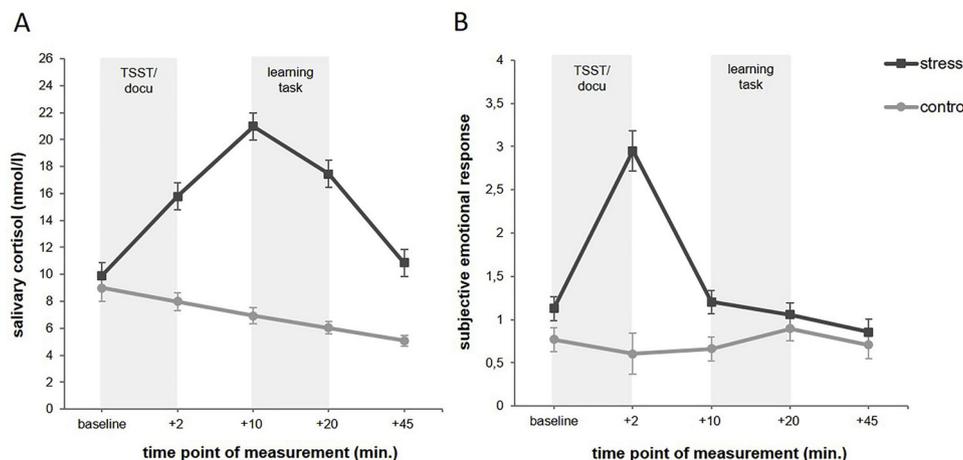


Fig. 1. Panel A shows mean (± SE) salivary cortisol concentration in dependence of treatment. Panel B illustrates mean (± SE) emotional stress assessed with the SERS. The treatment as well as the learning task are represented by a shaded area. *** $p < .001$; ** $p < .01$.

($F(2.48,141.08) = 15.37, p < .001, \eta^2 = .212$) was found, with a gradual improvement in learning performance during the task. When overall performance was analyzed, there were no significant main effects of treatment ($p = .186$) or learning strategy ($p = .132$), nor was there a treatment by learning strategy interaction ($p = .942$). Based on the above-mentioned findings with divergence in learning strategy between stress and control group over the course of the task, we further analyzed each block separately. In block 1 and 2 an univariate ANOVA exhibited a significant main effect of learning strategy (block 1: $F(1,57) = 11.78, p = .001, \eta^2 = .171$; block 2: $F(1,57) = 14.41, p < .001, \eta^2 = .202$) pointing at significant better performances on the part of NDL in comparison to DL. Furthermore in block 2 stressed participants reached better performances than controls on a trend level (main effect of treatment: $F(1,57) = 2.91, p = .093, \eta^2 = .049$). In block 3 there were no significant effects of treatment or learning strategy ($p < .126$). In block 4 a univariate ANOVA revealed a significant main effect of learning strategy ($F(1,57) = 7.60, p = .008, \eta^2 = .118$) and a learning strategy x treatment interaction ($F(1,57) = 6.12, p = .016, \eta^2 = .097$), with post-hoc tests showing a significantly better performance in stressed non-declarative learners compared to all other groups ($t(69.4) = -4.70; p < .001$; Fig. 2B). There were no difference in learning performance between the learning strategies under control condition ($p = .362$; Fig. 2B).

3.3. The relationship between stress measures and multiple memory systems

We further analyzed whether there was a treatment-dependent relationship between the hormonal as well as emotional stress measures and the used learning strategy. Binary logistic regressions showed that pre-stress salivary cortisol levels significantly predicted learning strategy in that higher cortisol levels in the stress group were associated with a greater probability to adopt a non-declarative learning strategy (treatment x cortisol_baseline: $B(1) = -.436, R^2 = .184, p = .047$; Fig. 3). No such association was observed in the control condition (all $p \geq .464$), and there were no associations between emotional stress and learning strategy (all $p \geq .541$).

3.4. The role of the MR polymorphism

3.4.1. Genetic analysis

For MR-2 G/C, genotyping via high-resolution melt analysis identified 19 participants homozygous for the C-allele, 13 participants homozygous for the G-allele and 38 heterozygotes. Genotyping of four samples was unsuccessful. The observed allele frequency were in Hardy-Weinberg equilibrium ($\chi^2(1,70) = .615, p = .433$). Homozygous

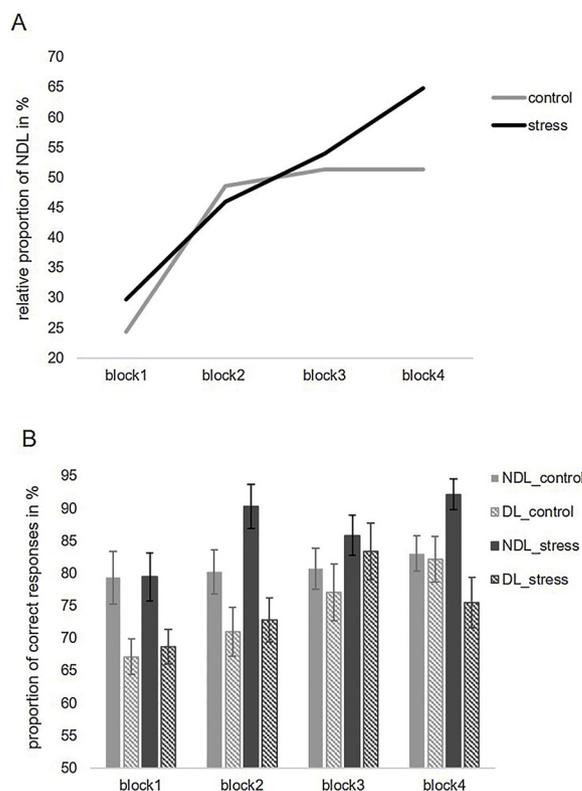


Fig. 2. Graphs in panel A represent the accumulated relative proportion of participants (stress and control group), who adopted a non-declarative learning strategy in dependence of blocks of 50 trials during the weather prediction task. Panel B shows mean (± SE) percentage of correct responses in dependence of learning strategy (non-declarative learner (NDL) vs. declarative learner (DL)) and stress (TSST vs. control). The data illustrates a stress-induced continuous increase in the number of NDL over the course of the learning task, associated with significant better learning performances under stress in block 4 compared to all other groups.

carriers of the C-allele were tested against G-carriers, leading to 12 C/C-, 23 G-carriers (18 C/G, 5 G/G) in the stress and 7 C/C-, 28 G-carriers (20 C/G, 8 G/G) in the control group. Chi-square tests showed that different genotypes are distributed randomly between the treatments ($p > .190$). Genetic variants were not significantly associated with age or BMI (both $p \geq .143$).

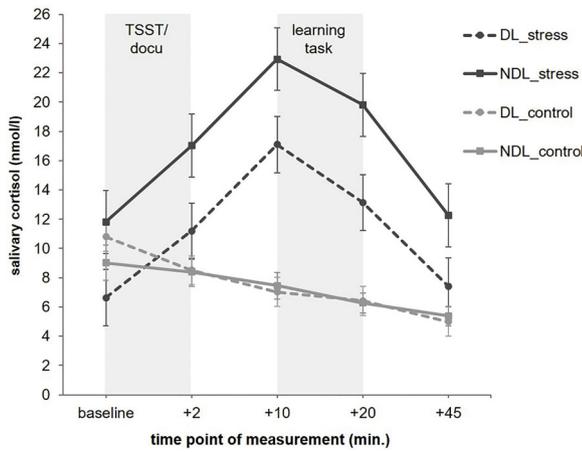


Fig. 3. Mean (\pm SE) salivary cortisol concentration with respect to different learning strategies (non-declarative learner (NDL) vs. declarative learner (DL)) for the control and stress group. The treatment as well as the learning task are represented by a shaded area. The magnitude of the anticipatory cortisol increase predicted the learning strategy in the weather prediction task.

3.4.2. Genetics and stress reactivity

As illustrated in Fig. 4A, a mixed ANOVA with rs2070951 and treatment as independent variables revealed that C/C-carriers tended to exhibit a stronger cortisol secretion than G-carriers (rs2070951: $F(1,63) = 3.90, p = .054, \eta^2 = .071$). Post-hoc mixed ANOVAs showed that under stress, C/C-carriers exhibited a significantly higher salivary cortisol concentration than G-carriers (rs2070951: $F(1,30) = 4.99, p = .034, \eta^2 = .084$), whereas no significant difference in cortisol between C/C- and G-carriers under control condition was detectable ($p > .113$). Analysis of every time point of measurement showed that the latter finding is mostly due to a significantly larger cortisol peak of C/C-carriers in comparison to G-carriers ($t(32) = 2.08, p = .045$). There were no differences in salivary cortisol regarding other time points of measurement (all $p \geq .313$). With respect to emotional responses, mixed ANOVAs exhibited neither a main effect of rs2070951 ($p = .166$) nor a rs2070951 x treatment interaction ($p = .60$; Fig. 4B).

3.4.3. Genetics and stress effects on multiple memory systems

There was no association between rs2070951 and choice of learning strategy ($\chi^2(2, 62) = 2.057, p = .358$). However, we found a

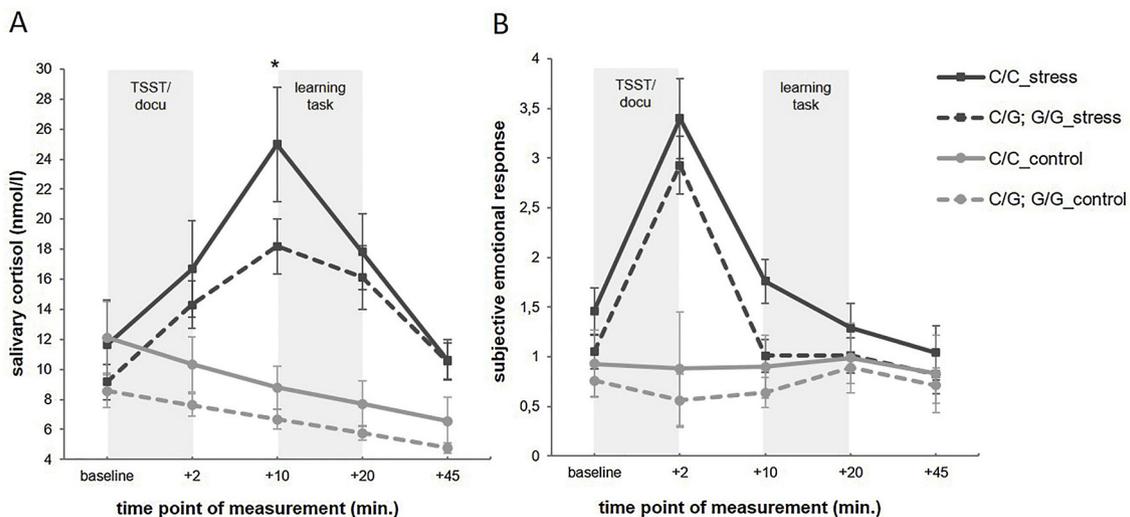


Fig. 4. Graphs in panel A show mean (\pm SE) progress of salivary cortisol concentration whereas panel B illustrates mean (\pm SE) progress of emotional stress in dependence of variants of rs2070951 (C/C-carriers vs. G-carriers) with respect to control and stress group. The stress induction and the learning task are represented by shaded areas. C/C-carriers exhibited a significant larger stress-induced cortisol peak than G-carriers. ** $p < .01$; * $p < .05$.

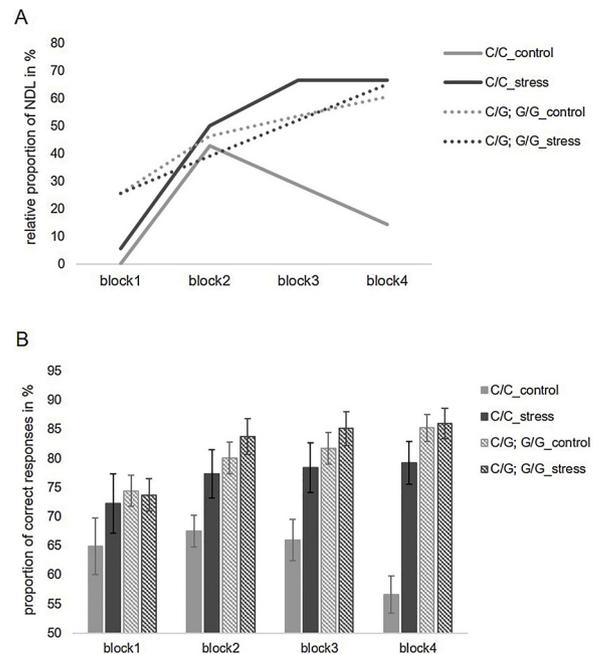


Fig. 5. Graphs in panel A represent the accumulated relative proportion of participants separated for treatment (stress vs. control) and rs2070951 (C/C vs. C/G; G/G), who adopted a non-declarative learning strategy in dependence of blocks of 50 trials during the weather prediction task. Bars in panel B show mean percentage of correct responses (\pm SE) in dependence of variants of rs2070951 (C/C vs. C/G; G/G) and treatment (stress vs. control). C/C-carriers of the control group exhibited significant less NDL in block 4 and a significant worse learning performance in comparison to all other participants.

significant association between the MR SNP and learning strategy in block 4 ($\chi^2(1,35) = 4.83, p = .028$; Fig. 5A) under control condition. C/C-carriers in the control group less often switched to a non-declarative learning strategy than G-carriers, whereas no difference between genotype with respect to learning strategy was observed in the stress group (all $p > .410$). With regard to learning performance, C/C-carriers performed worse than G-carriers (rs2070951: $F(1,65) = 8.20, p = .006, \eta^2 = .112$; Fig. 5B). Post-hoc t-tests showed that the latter effect was restricted to the control group ($t(32) = -.271, p = .011$), whereas no significant difference in learning performance between

variants of rs2070951 were observed under stress condition ($p = .245$).

4. Discussion

Stress has been shown to induce a shift in the use of declarative to non-declarative memory systems. The present study showed that compared to a control condition stress exposure was associated with a continuous increase in the use of a non-declarative strategy in a probabilistic classification learning task. The shift toward a non-declarative strategy resulted in better learning performance, which suggests that the observed shift was adaptive. In addition, higher pre-stress cortisol levels were associated with a higher probability to adopt a non-declarative learning strategy. Genetic data revealed an association between a common *MR* SNP and HPA axis activity as well as learning performance. rs2070951 C/C-carriers exhibited a stronger stress-induced cortisol secretion than G-carriers. Beyond that, C/C-carriers in the control group less often switched to a non-declarative learning strategy, which was associated with poorer learning performances, whereas no such differences could be found in the stress group.

The present findings are consistent with a growing literature showing that stress prompts rigid, habitual behavior through the non-declarative memory system (Fournier et al., 2017; Goldfarb et al., 2017; Quaedflieg and Schwabe, 2018; Schwabe and Wolf, 2012a, 2013; Wirz et al., 2017a, 2017b; Wirz et al., 2018). Given that stress continuously favored the adoption of a non-declarative learning strategy, which resulted in better learning performances, the present data supports the assumption of an adaptive modulation of multiple memory systems under stress (Schwabe and Wolf, 2013; Vogel et al., 2016). Unconscious routines provided by the non-declarative memory system require little cognitive effort (Squire, 2004). Hence, the dominance of the non-declarative memory system under stress may represent an adaptation in order to facilitate coping (Schwabe et al., 2013). Besides, the present results are in line with the idea of interacting memory systems (Poldrack et al., 2001), which cooperate or compete with each other in order to supply maximal resources to the organism. Imaging data supports the latter idea, showing that stress led to increased striatal and reduced hippocampal activity (Wirz et al., 2017a, 2017b). Stress dynamically changes the processing of memory-related brain areas in order to adapt to a stressful event allowing highly efficient processing (Quaedflieg and Schwabe, 2018; Vogel et al., 2016). Thus, stress seems to play a crucial role in coordinating the interaction of multiple memory systems in an adaptive manner. Interestingly, at the end of the learning task stressed NDL achieved better performances than all other participants. Not only does stress promote habitual, less demanding learning behavior (Schwabe and Wolf, 2012b), but it might also enhance the efficiency of the non-declarative memory system. Previous research already provided evidence for an association between the non-declarative system and learning performance under stress (Schwabe and Wolf, 2013). Whereas in stressed participants, success in the PCL task significantly correlated with striatal activity, no such correlation was found under control condition. Thus, present findings may be indicative of an improvement of the non-declarative memory system under stress probably mediated by glucocorticoid actions (Vogel et al., 2017) resulting in better learning performances.

Even though the precise mediating function of cortisol is still controversial (e.g. Wirz et al., 2017a, 2017b), several researchers postulated an HPA axis reactivity-dependent shift in the dominant memory system (Smeets et al., 2018; Vogel et al., 2017). Our results underscore the latter idea providing evidence for a relationship between stress-induced HPA axis reactivity and strategy use. Higher pre-stress cortisol levels were related to a more pronounced use of a non-declarative learning strategy. Since the participants were already informed about the experimental condition 10 min prior to the treatment, pre-stress increase in salivary cortisol concentration might be explained by an anticipatory HPA axis response. Therefore, anticipatory stress-related HPA axis activity seems to favor the non-declarative memory system.

Participants vary in their anticipatory stress response (Engert et al., 2013), which could be a predictive factor of cognitive adaptability. In view of the anticipatory stress response accounting for variance in psychological health (Engert et al., 2013), the results might also explain individual differences in cognitive flexibility. Schwabe and colleagues (2012) argued that glucocorticoids interact in the basolateral amygdala to facilitate the consolidation of stressful experiences. Thus, glucocorticoids enable the amygdala to orchestrate the engagement of multiple memory systems adaptively (Packard and Wingard, 2004; Schwabe and Wolf, 2012a; Vogel et al., 2015). The data confirm a positive relationship between stress-induced HPA axis reactivity and the dominance of the non-declarative memory system enabling an adaptive organization of learning behavior under stress (Goldfarb et al., 2017; Smeets et al., 2018). The latter findings raise the question, which factors contribute to HPA axis reactivity explaining individual differences in the engagement of multiple memory systems under acute stress. Several studies suggested a relationship between *MR* gene variation and HPA axis activity (DeRijk and de Kloet, 2008; Li-Tempel et al., 2016; Taylor et al., 2014; van Leeuwen et al., 2010, 2011; Wirz et al., 2017a). The *MR-2C* variant was related to a higher transcriptional activity (van Leeuwen et al., 2010) as well as to a more pronounced protein expression resulting in an increased secretion of cortisol (van Leeuwen et al., 2011). In line with previous research, the present data revealed a relationship between *MR-2G/C* and the magnitude of stress-related HPA axis activity. Participants homozygous for the C-allele showed a stronger stress response than G-carriers. Therefore, the results of Taylor and colleagues (2014) support the notion of a stimulating effect of *MR-2C* on HPA axis under stress. The rs2070951 polymorphism might modulate the transcription of the *MR* reinforcing a dynamic reactivity of the stress systems (van Leeuwen et al., 2011). Accordingly, the present study is in line with the notion that the *MR-2G/C* polymorphism influences individual differences in stress-responsivity and coping style, probably affecting vulnerability to diseases (DeRijk and de Kloet, 2008).

Our study provides suggestive evidence for a relationship between variants of one *MR* polymorphism (*MR-2G/C*) and the influence of stress on the engagement of multiple memory systems (Fig. 6). Whereas G-allele carriers continuously increased in their use of a non-declarative learning strategy under both the stress and the control condition, carriers of the C/C genotype preferentially adopted the non-declarative learning strategy under stress only. Furthermore, the use of a declarative strategy, i.e. the failure to switch strategies, was associated with poorer learning performance, suggesting a beneficial effect of stress for this type of learning task, which is dependent on *MR* gene variation. Apparently, C/C-carriers - in contrast to G-carriers - were not able to update their learning strategy by the given feedback resulting in a missing improvement of learning performance over the course of the task. Therefore, present data hints at *MR* gene variation as a factor explaining individual variability in the engagement of multiple memory systems accounting for differences in learning performance. C/C-carriers seem to be reliant on stress initializing the shift towards the non-declarative memory system in order to reach similar learning performances. Since C/C-carriers exhibited a greater stress-induced cortisol secretion than G-carriers, genetic data further support the idea of a crucial role of cortisol facilitating beneficial learning behavior (Smeets et al., 2018; Vogel et al., 2017). Collectively, stress seems to compensate the lack of adaptability to task demands rescuing learning performance (Schwabe et al., 2013) in C/C-carriers probably favored by an increased HPA axis response. Notably, a recent report determined that variants of a common *MR* haplotype (rs2070951 [*MR-2G/C*] & rs5522 [*MR-I180V*]) facilitates a stress-induced shift from hippocampal toward dorsal striatal learning (Wirz et al., 2017a). In carriers of the CA haplotype, stress led to an increase in the use of multi-cue (non-declarative) strategies while the shift was absent in non-carriers. Supporting the latter finding, carriers of the CA haplotype showed a reduced hippocampal activity under stress indicating a reduced

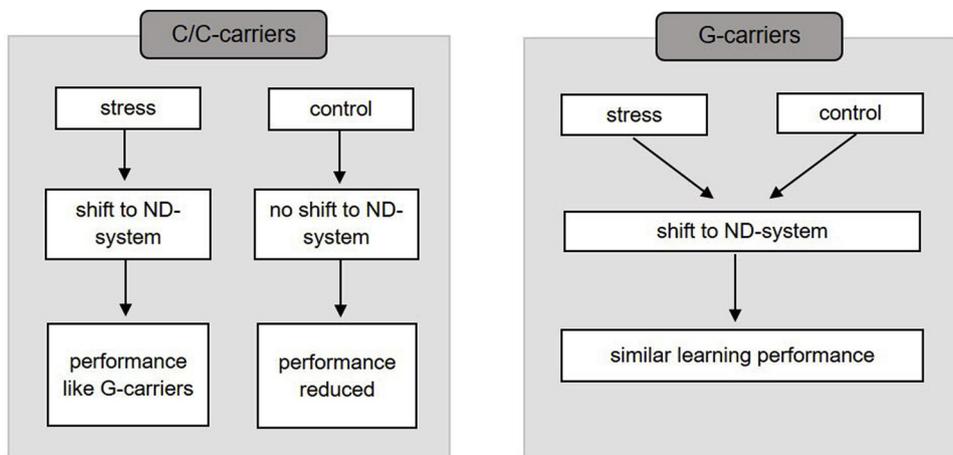


Fig. 6. Graphical illustration of the postulated relationship between variants of *MR-2 G/C*, shift to the non-declarative memory system (ND-system) as well as learning performance in comparison to control participants. C/C-carriers preferentially adopted a non-declarative strategy under stress only, whereas G-carriers continuously switched to the non-declarative system independent of stress. The failure to switch to the non-declarative system resulted in poorer learning performances.

processing in cognitive areas. Accordingly, the C-allele of rs2070951 might be at least one factor explaining individual variability in the shift towards less cognitive demanding habitual behavior under stress. The present data are consistent with the latter hypothesis in that emphasizing a relationship between C/C-carriers and stress-induced shifting toward the non-declarative system. Thus, the MR-2C variant might favor the adaptive engagement of multiple memory systems under stress. These results underline the critical involvement of the MR in generating adaptive learning behavior under stress (Schwabe et al., 2013; Vogel et al., 2016). Previous research has already indicated that genetic polymorphisms contribute to individual differences in human memory performance and memory-related brain activations (de Quervain and Papassotiropoulos, 2006). Given several hints toward MR-2 G/C dependent differences in learning performance under stress, future research is needed to further investigate the relationship between variants of *NR3C2* and the influence of stress on learning performance. Since C/C-carriers displayed a more pronounced stress-reactivity (van Leeuwen et al., 2010, 2011), the present data advocates that the gene dependent differences in the involvement of multiple memory systems under stress might be explained by variations in stress sensitivity (Ter Heegde et al., 2015). Taken together we suggest that a common functional SNP on the MR gene (rs2070951) represents an important factor explaining individual differences in the adaptive organization of learning behavior under stress.

Following limitations need mention. A direct comparison with previous reports can only be performed at the conceptual level, as previous studies used different stress induction methods (TSST: Fournier et al., 2017; CPT: Goldfarb et al., 2017; SECPT: Schwabe and Wolf, 2012a; MAST: Smeets et al., 2018) as well as learning tasks (sequential decision making task: Otto et al., 2013; weather prediction task: Schwabe and Wolf, 2012a; outcome devaluation task: Smeets et al., 2018). In contrast to prior studies, which used the weather prediction task, no significant (Schwabe et al., 2013; Schwabe and Wolf, 2012a) overall effect of stress on learning strategy was found. This could be due to methodological differences as well as varying sample characteristics. For instance, most studies included both sexes (Schwabe et al., 2013; Schwabe and Wolf, 2012a; Wirz et al., 2017a), whereas we focused on male participants only. Another influencing factor could have been individual differences in prenatal stress (Schwabe et al., 2012a,b). In addition, the association of cortisol and strategy use is based on an anticipatory stress response. In future studies it might be worth to investigate whether individual differences in HPA axis activity predicts the learning strategy if participants are not informed by the condition prior to the testing.

The present study is also limited by its sample size, which was responsible for relative small group sizes regarding the three factors (stress, learning strategy and gene variants). Whereas the present study was adequately powered to detect effects of stress on learning outcomes

(power $(1-\beta) = 0.712$), the genetic analyses have to be regarded as purely exploratory due to the small size. Furthermore, the small sample size precluded us from genotyping for the relatively infrequent MR SNP rs5522 (minor allele frequency 11.8%), which would have been necessary for haplotype based analysis (de Kloet et al., 2016). In addition, the study lacks a physiological measurement of the autonomic nervous system (ANS) activity. Since the ANS might also be affected by genetic variation (Wirz et al., 2017b), indicators of the ANS activity could also be one factor explaining individual differences in the learning strategy. Different variants of the MR gene can have opposite effects in males and females (van Leeuwen et al., 2010), and future work should investigate possible sex-specific effects.

In conclusion, our results support the notion of a critical role of cortisol in initializing an adaptive shift from declarative to non-declarative learning strategies following stress exposure, and further point toward the MR as an important mediator of stress-induced effects of HPA axis reactivity on learning behavior

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.psyneuen.2019.05.006>.

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