

Frontal Control Over Automatic Emotional Action Tendencies Predicts Acute Stress Responsivity

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ABSTRACT

BACKGROUND: The ability to control social-emotional actions is relevant for everyday social interaction and may be indicative of responsiveness to actual social stress situations. This is particularly relevant for predicting stress responsiveness of the hypothalamic-pituitary-adrenal axis, known to be dysregulated in various stress-related affective disorders. Here we tested, in a large sample, whether reduced frontal control over social approach-avoidance actions can indeed signal increased hypothalamic-pituitary-adrenal axis reactivity to subsequent social stress exposure.

METHODS: A total of 279 subjects (214 men) participated in a functional magnetic resonance imaging social-emotional approach-avoidance task that involved impulsive and controlled emotional actions. Subsequently, participants underwent a stress induction including a socially evaluated cold pressor task and a mental arithmetic task. Salivary cortisol and α -amylase levels, as well as self-reported negative affect, were measured before and after stress induction.

RESULTS: Emotion control was successfully induced by the approach-avoidance task. Namely, instrumental overriding of automatic social approach-avoidance actions was associated with the typical increased bilateral anterior prefrontal cortex activation, longer reaction times, and more errors. Moreover, subsequent stress induction led to significant increases in all stress measures. Critically, bilateral anterior prefrontal cortex activation during emotion control was associated with reduced responses to the subsequent stressor in not only cortisol but also α -amylase and negative affect.

CONCLUSIONS: The ability to recruit prefrontal regions during social-emotion regulation predicts cortisol responses to an actual social stress situation. This finding provides the first evidence that instrumental control over social approach avoidance actions can signal stress responsiveness in major stress systems, providing a promising biomarker in stress vulnerability and resilience research relevant for affective disorders.

Keywords: Approach-avoidance behavior, Cortisol, Emotion regulation, Neuroimaging, Prefrontal cortex, Stress response

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Healthy social-emotional behavior in everyday social interactions involves adequate control over automatic responses to affective cues such as emotions expressed by others (1). This largely prefrontally driven emotion control becomes particularly relevant during socially threatening situations, when control over highly salient social cues is essential to prevent the major stress systems from overshooting. Failure of this emotion control and dysregulation of these stress systems are implicated in a broad range of psychopathologies (2,3). Although these notions are widely adopted in human stress theories (4), direct neurocognitive evidence for the link between frontal emotion control capacities and glucocorticoid stress responsiveness is lacking, let alone evidence in well-powered samples.

Acute stress results in fast responding of the sympatho-adrenomedullary system, increasing noradrenaline, and activation of the hypothalamic-pituitary-adrenocortical (HPA) axis, with its end product cortisol. Particularly the slower-acting HPA system is implicated in returning to homeostasis and is seen as an adaptive process, impairments of which are associated with psychopathology such as depression, post-traumatic stress disorder, and anxiety disorders (5–12). Both chronic and acute stress impair prefrontal functioning (13,14). Impaired prefrontal functioning, in turn, plays an important role in the pathophysiology of affective disorders, including depression and anxiety (15,16).

Crucially, the link between stress and prefrontal functioning is not unidirectional; the prefrontal cortex (PFC) not only is

impaired as a function of acute and chronic stress but also plays a role in the regulation of the HPA axis and thus the glucocorticoid stress response (17–19). However, the neurocognitive evidence on this latter process (i.e., reduced PFC functioning as a predisposing factor for maladaptive stress responsivity) is limited. Interestingly, a recent study found a link between reduced PFC activation and increased cortisol after stress both in patients with depression and in healthy participants (20). Because PFC activation was measured during stress induction, however, it is likely to be influenced by feedback mechanisms triggered by the stress response, so it remains unclear whether PFC activation can serve as a neurocognitive predictor of HPA axis function.

In this study, we tested whether PFC activation during a relevant social-emotion regulation task predicts cortisol stress responsiveness during social stress in a well-powered sample ($N = 283$, 76% men) of medication-free healthy participants. This approach allows for a mechanistic understanding of variability in HPA axis functioning in the healthy population, which could then serve as a starting point for further investigations in clinical populations (21). Although there are different types of emotion regulation, they all rely on control of the PFC over regions primarily involved in emotional reactivity such as the amygdala (1,22). We employed a functional magnetic resonance imaging (fMRI)-optimized approach-avoidance (AA) task, measuring social-emotion control over automatic action tendencies, which has been shown to robustly activate the anterior subregion of the PFC (aPFC) (23–26). Stress was induced by a socially evaluated cold pressor task (SECT) and a mental arithmetic (MA) task. We hypothesized that relatively low aPFC activation during emotional action regulation is associated with relatively stronger cortisol increases after subsequent stress induction. As secondary stress indices, we used increases in salivary α -amylase, which is a marker of sympatho-adrenomedullary activity (27) and self-reported negative affect, as measure of a subjective stress response.

METHODS AND MATERIALS

Participants

A total of 427 participants passed initial screening. Exclusion criteria were current psychiatric and neurological disorders, a history of endocrine or neurological treatment, current drug or alcohol abuse, and current use of psychotropic medication. Complete datasets were available for 305 participants. Participants with anatomical abnormalities or poor MRI quality, excessive movement during MRI acquisition (i.e., maximal framewise displacement >3 mm), extreme scores on hormone variables [outliers $> |3.29|$ SD (28)], or poor task performance (i.e., <10 correct trials in one or more of the four task conditions) were excluded. Consequently, the final analyses comprised 279 participants (214 men) between 18 and 43 years of age (median = 23 years). Of the final sample, 80% ($n = 226$, 176 men) were students from the Dutch Police Academy, and the remainder were students from other schools and universities. The latter were age and gender matched to the police recruits and included in all analyses because no systematic differences in the relationship between prefrontal control and stress responsivity were expected between those students, which was

confirmed by later analyses (see Supplemental Table S1). α -Amylase and negative affect analyses were performed on subgroups (see Supplement). To test the effectiveness of the stress induction procedure, we also tested a separate nonstress group ($n = 25$, 18 men). The study was conducted in accordance with the Declaration of Helsinki and approved by the Independent Review Board Nijmegen (Nijmegen, The Netherlands).

Procedure

All reported experiments were conducted as part of the baseline measurement of a prospective study assessing the role of automatic defensive responses in the development of trauma-related psychopathology in police recruits (Netherlands Trial Registry NTR6355). See Koch *et al.* (29) for details. On arrival in the lab, participants provided written informed consent, completed several questionnaires, performed several behavioral and fMRI tasks (not reported here), and underwent a 7-minute structural T1-weighted scan. Approximately 1 hour before the AA task, a baseline saliva sample was collected for baseline hormonal assessments (see Supplement for details on the analysis of the baseline cortisol and testosterone samples). In the MRI scanner, participants completed a 3-minute AA task training session, which was followed by the AA task (12 minutes). Subsequently, participants underwent a resting-state scan, the stress induction, and a second resting-state scan (resting-state data not discussed here). During the procedure (see Figure 1A), saliva and a negative affect questionnaire (Positive and Negative Affect Schedule) (30) were collected five times with intervals of approximately 10 minutes. See Supplement for more details on the saliva sample collection. The AA task and the stress induction were conducted in the late afternoon between 4 and 7 PM when diurnal effects on cortisol fluctuations are minimal (31).

Experimental Task

The AA task is a well-established task (23,32,33), requiring participants to respond as fast as possible to pictures of facial expressions by moving a joystick (Figure 1B). The automatic tendency is to approach happy faces and avoid angry faces (affect-congruent actions). Execution of the opposite (affect-incongruent actions) requires control over these automatic action tendencies, reflected in longer reaction times and stronger aPFC recruitment (32,33). At the start of congruent blocks, participants were instructed to pull the joystick in response to happy faces and to push it in response to angry faces. The instruction was reversed for incongruent blocks. There were 4 congruent and 4 incongruent blocks (12 trials each) presented alternately, with a counterbalanced starting block type, an interblock interval of 21 to 24 seconds, and an intertrial interval of 2 to 4 seconds. The facial expressions (36 models [18 male], two emotions each) originated from multiple databases (34–37). Presentation software version 16 (<https://www.neurobs.com>) was used for stimuli presentation and the acquisition of joystick positions. See Tyborowska *et al.* (38) for details.

Stress Induction

Stress induction consisted of two sequentially administered tasks, a SECT and an MA task, which have been shown to

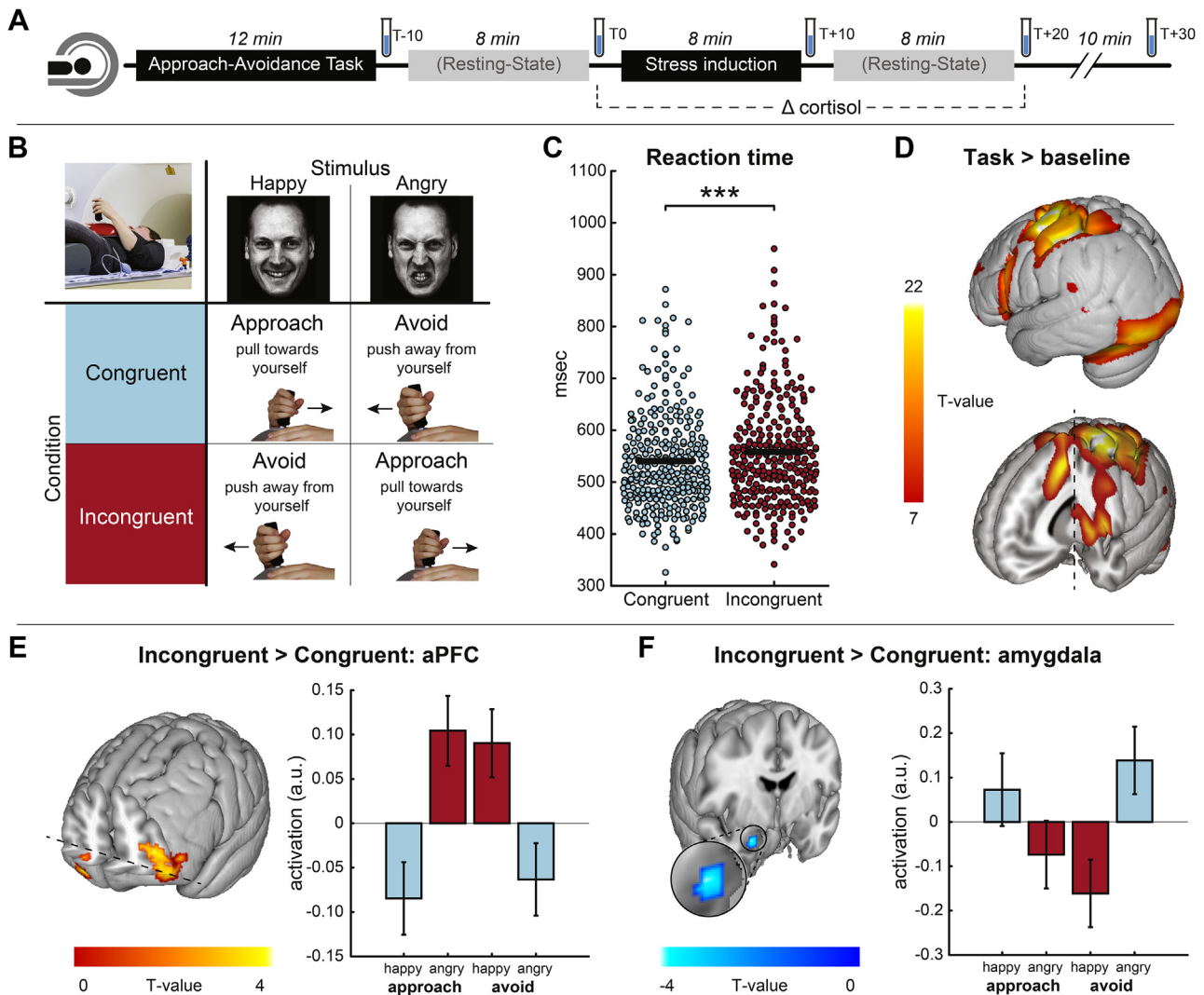


Figure 1. (A) Schematic timeline of the experimental procedure. (B) Response mapping for the different conditions during the approach-avoidance task. (C) Responses in the incongruent condition were significantly slower than those in the congruent condition. (D) Overview of regions showing increased activation across all task conditions. (E, F) Activation differences between the incongruent and congruent task conditions for the a priori defined regions of interest: the bilateral anterior prefrontal cortex (aPFC) and amygdala. Small volume corrected results at an initial threshold of $p < .005$ are shown. Only clusters with peak activation within one of the volumes of interest are displayed. Bar graphs visualize beta estimates of the effects for each task condition extracted from the bilateral activation clusters. Sample images are AM10HAS and AM10ANS from the Karolinska Directed Emotional Faces stimulus set (36). *** $p < .001$. a.u., arbitrary units.

successfully induce psychophysiological and subjective stress responses (39–41). Both tasks lasted for 3 minutes, but participants were not informed about the exact duration. Two experimenters closely monitored their facial expressions. At least one of them was of the opposite gender of participants to ensure maximal social stress (42). The primary experimenter was unfamiliar to participants, wore a white lab coat, and spoke in a formal manner. The assistant experimenter was familiar to participants because he or she had instructed participants during all other experimental procedures. During the SECPT, the primary experimenter instructed participants to immerse their right foot in ice-cold water (0–3°C), to lie as still as possible, and not to talk. During the subsequent MA task, the primary experimenter instructed participants to count back

out loud from 2059 in steps of 17 as quickly and accurately as possible. The primary experimenter gave feedback when the counting went slow. After each error, participants were asked to start over from 2053, 2045, or again 2059. The full procedure took approximately 8 minutes including instructions. A separate sample of 25 participants completed a control (nonstress) procedure (see Supplement).

Analysis of Questionnaire and Hormone Levels

All stress-response measures were log transformed to correct for a skewed distribution and entered into separate repeated-measures analyses of variance with sampling time as the independent variable, followed by Bonferroni-corrected

paired-sample *t* tests testing for differences between sampling times. These analyses were performed on a subsample of all participants (cortisol $n = 244$, α -amylase $n = 222$, negative affect $n = 255$) because of incomplete data or detection problems. To link the stress response measures to the AA task behavioral and neural effects, we calculated difference scores for each measure (Δ -cortisol, Δ - α -amylase, and Δ -negative affect) by subtracting the log-transformed value of the pre-stress-induction sample (T_0) from the peak post-stress-induction sample. Individuals with extreme values [$>|3.29|$ SD (28)] for the difference scores for any stress measure within each gender group were excluded from the respective analyses. Outliers were determined for each gender separately because the strength of the cortisol increase differs per gender (43). Comparison with a nonstress group enabled a manipulation check for the stress induction and indicated significantly greater Δ -cortisol and Δ -negative affect in the stress group (all p s $< .001$), but not for Δ - α -amylase ($t_{277} = 1.20$, $p = .232$) (see Supplemental Table S1).

Behavioral Analysis

See Supplement for details on behavioral data preprocessing. Mean reaction times and error rates were entered into two separate repeated-measures analyses of variance with within-subject factors movement (approach or avoid) and valence (happy or angry). Gender and Δ -cortisol were included as covariates. Analyses were repeated with Δ - α -amylase and Δ -negative affect as covariates instead of Δ -cortisol. The alpha level was set at .05.

fMRI Single-Subject Analysis

See Supplement for details on imaging parameters and the preprocessing of the 3T fMRI data. Following Volman *et al.* (33) and Tyborowska *et al.* (38), the fMRI time series were analyzed using an event-related approach within the framework of the general linear model. The following effects were considered separately: approach-happy, approach-angry, avoid-happy, and avoid-angry. The time of stimulus presentation (onset) and the time between stimulus presentation and response (duration) were convolved with the canonical hemodynamic response function. Misses and on-screen information (instructions preceding each block and feedback messages) were modeled as separate regressors. Potentially confounding effects of residual head movement were modeled using original, squared, cubic, first-order, and second-order derivatives of the movement parameters (44). Three further regressors described the time course of signal intensities of white matter, cerebrospinal fluid, and the portion of the magnetic resonance image outside the skull (45). The fMRI time series were high-pass filtered (cutoff of 128 seconds). Temporal autocorrelation was corrected by a first-order autoregressive model.

fMRI Second-Level Analyses

To assess overall task effects (task performance $>$ baseline), contrast images of a combination of all four task conditions (approach-happy, approach-angry, avoid-happy, and avoid-angry) were entered into a random-effects multiple regression analysis.

For the main analysis, contrast images of the four task conditions were entered into a random-effects multiple

regression analysis separately for each condition. Subject-specific regressors were added to control for overall between-subject effects. We first contrasted affect-incongruent trials (approach-angry and avoid-happy) with affect-congruent trials (approach-happy and avoid-angry). Subsequently, Δ -cortisol values, log-transformed baseline testosterone levels, and log-transformed baseline cortisol levels were standardized within each gender group and added as condition-specific covariates, yielding 12 extra regressors. Baseline cortisol and testosterone levels were added to remain consistent with previous work (33,38). We assessed the interaction of these congruency effects with stress responsivity, indexed by Δ -cortisol, by contrasting the condition-specific covariates (Δ -cortisol happy-approach + Δ -cortisol angry-avoid vs. Δ -cortisol happy-avoid + Δ -cortisol angry-approach). This analysis was repeated with Δ - α -amylase and Δ -negative affect instead of Δ -cortisol.

Effects were assessed at the whole-brain level and within a priori defined regions of interest that have been shown to be sensitive to AA task congruency effects (33,46): the bilateral aPFC based on the lateral frontal pole region from a frontal cortex parcellation atlas (47) and the bilateral amygdala based on the automated anatomical labeling atlas (48). The reported activation clusters were corrected for multiple comparisons using a familywise error (FWE) correction. Statistical inferences were made at the peak level for both the whole-brain analyses (FWE $p < .05$) and the volumes of interest (small volume correction [SVC], FWE $p < .05$, initial cluster-forming threshold $p < .005$). Anatomical inference was drawn by superimposing the thresholded SPM T-maps onto the canonical SPM single-subject T1 image.

RESULTS

Regulation of Approach-Avoidance Behavior

In line with previous findings (23,32,49), participants responded slower and made more errors during trials that required a response incongruent with the automatic tendency (i.e., approaching angry faces and avoiding happy faces) compared with congruent trials (valence $\times$ movement interaction reaction time: $F_{1,271} = 17.43$, $p < .001$; error rate: $F_{1,271} = 20.91$, $p < .001$) (Figure 1C). This indicates that participants had greater difficulty in performing the required actions during incongruent trials. Gender, education type (police or nonpolice), and Δ -cortisol, Δ - α -amylase, or Δ -negative affect did not modulate these behavioral effects. See Supplement for more details.

Overall, task performance recruited a network including, among other regions, the primary motor cortex, supplementary motor cortex, occipital cortex, and frontal cortex (Figure 1D). As expected (33,46,50,51), participants showed increased bilateral aPFC activation during the incongruent condition (i.e., approach-angry and avoid-happy) compared with the congruent condition (i.e., approach-happy and avoid-angry), reflecting increased recruitment of this frontal region to control automatic emotional response tendencies (left: local maxima $x, y, z = -32, 54, 6$, SVC $p_{FWE} = .013$; right: local maxima $x, y, z = 18, 60, -6$, SVC $p_{FWE} = .048$) (Figure 1E). Conversely, participants showed decreased right amygdala activation during the incongruent condition compared with the congruent condition (local maxima $x, y, z = 24, -2, -20$, SVC

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$p_{\text{FWE}} = .045$) (Figure 1F). This is in accordance with the supposed mechanism of frontal control over the amygdala during emotion control. See Supplement and Supplemental Table S2 for whole-brain congruency effects, which included increased activation in the inferior parietal lobe, lateral orbital frontal cortex, and precuneus. No effects of valence were found on the whole-brain level or within the volumes of interest.

Stress Manipulation

Stress levels changed significantly over time for all measures during the subsequent stress induction procedure (main effect sampling time: cortisol, $F_{1,40,339.27} = 132.9$, $p < .001$; α -amylase, $F_{3,49,761.88} = 92.8$, $p < .001$; negative affect, $F_{2,90,736.82} = 83.7$, $p < .001$) (Figure 2). Before stress, cortisol showed a downward trend in line with the diurnal rhythm (T_{-10} vs. T_0 , $p < .001$) (31). In line with the usual timing of cortisol effects (52), cortisol levels did not increase immediately after the stress induction onset (T_0 vs. T_{+10} , $p = .792$) but were raised 20 and 30 minutes after stress (all p s $< .001$). α -Amylase levels and negative affect scores increased immediately after stress induction (T_0 vs. T_{+10} , all p s $< .001$). Thus, stress induction resulted in significant stress responses for all measures in the previously reported time-delineated fashion (52). See Supplement for a description of paired comparisons of the α -amylase and negative affect values for each time point. For all following analyses, we took the baseline to peak measures as an index of stress responsiveness: Δ -cortisol ($T_{+20}-T_0$), Δ - α -amylase ($T_{+10}-T_0$), and Δ -negative affect ($T_{+10}-T_0$).

Linking Emotional Action Control to Stress Sensitivity

We next assessed whether the neural markers of the approach-avoidance task could predict stress responsivity after the social stress induction. In line with our expectations, participants showing relatively smaller bilateral aPFC involvement during emotional action control (incongruent > congruent) responded to the stress induction with a relatively stronger cortisol increase (left: local maxima $x, y, z = -40, 52, -10$, SVC $p_{\text{FWE}} = .039$; right: local maxima $x, y, z = 24, 62, 12$, SVC $p_{\text{FWE}} = .044$) (Figure 3). Similar results were found for the other stress measures: α -amylase (left: local maxima $x, y, z = -24, 58, 6$, SVC $p_{\text{FWE}} = .025$; right: local maxima $x, y, z = 36, 50, -12$, SVC $p_{\text{FWE}} = .001$) and negative affect (left: local maxima $x, y, z = -22, 64, 2$, SVC $p_{\text{FWE}} = .003$; right: local maxima $x, y, z = 18, 64, 4$, SVC $p_{\text{FWE}} < .001$) (Supplemental Figure S1). See Supplemental Table S3 for all whole-brain stress-response-related effects, including a parahippocampal/amygdala cluster. No modulating effects of valence in general were found on the whole-brain level or within the volumes of interest.

In line with previously reported gender differences in cortisol stress reactions (43), Δ -cortisol was higher for male subjects than for female subjects within the stress group (Welch's $t_{239,56} = 10.52$, $p < .001$) (Supplemental Table S1). Therefore, we explored gender effects in the bilateral aPFC clusters showing cortisol-related activation differences by comparing the strength of the correlation between Δ -cortisol values and extracted contrast estimates from the bilateral aPFC clusters between male and female subjects. Both male and female

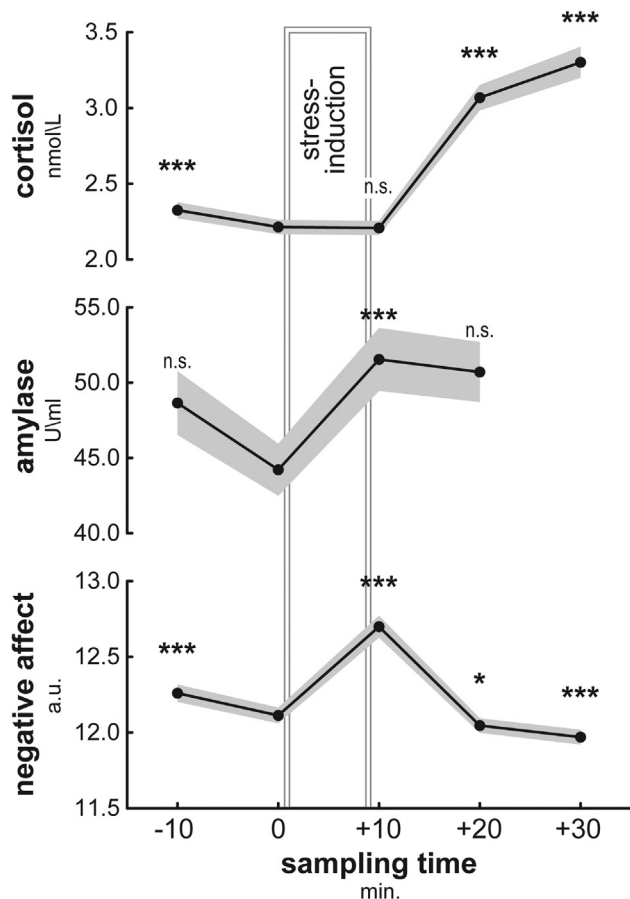


Figure 2. Response to stress induction as measured by salivary cortisol, salivary α -amylase, and self-reported negative affect. For visualization purposes, the last sampling point of the α -amylase is not shown here (see Results section). Gray areas represent standard errors. Asterisks indicate significance of the follow-up t test between the log-transformed values right before the stress induction (0 sampling time) and other time points. n.s., not significant; * $p < .05$; *** $p < .001$. a.u., arbitrary units.

subjects showed the negative association between differential aPFC activation and cortisol response (all p s $< .025$), but the magnitude of the correlation coefficient was greater for female subjects (Fisher's $z = 3.304$, $p < .001$). Female subjects who were using oral contraceptives ($n = 45$) showed a smaller cortisol response than female subjects who were not using hormonal contraceptives ($n = 11$) ($t_{54} = -2.143$, $p = .037$), but the association between cortisol response and aPFC activation was not significantly different between these female participants (Fisher's $z = -1.40$, $p = .16$). Interestingly, cortisol responses correlated to trait anxiety in female subjects ($r = .324$, $p = .008$) (see Supplemental Figure S2) and not in male subjects ($r = -.045$, $p = .517$; male vs. female subjects Fisher's $z = 3.91$, $p < .001$). For the α -amylase and negative affect findings within the aPFC, we did not find significant gender differences (all p s $> .13$).

Given the role of the amygdala in neurocognitive models of both emotion regulation and stress (1,13), we investigated whether cortisol increases were predicted by increased amygdala activation or reduced aPFC-amygdala connectivity

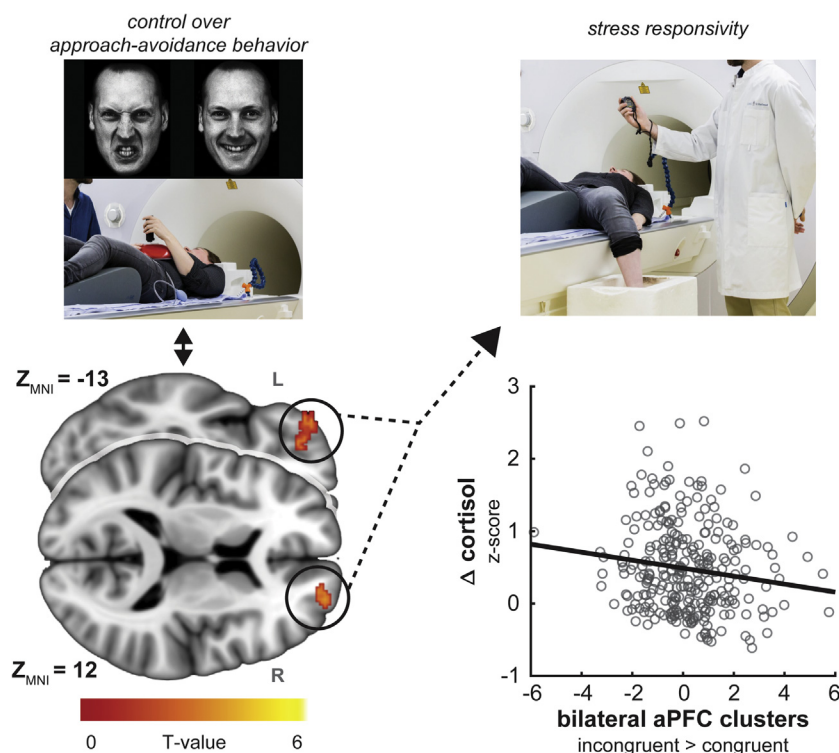


Figure 3. Bilateral anterior prefrontal cortex (aPFC) activation during the control over approach-avoidance behavior was negatively associated with cortisol responsivity after stress (T values of the brain clusters refer to the emotion control [incongruent > congruent] × stress response interaction). The scatterplot visualizes the mean bilateral cluster activation value in relation to the standardized cortisol increase (Δ -cortisol) for each subject. The relationship remained significant after removal of the most negative value on the x-axis. Small volume corrected results at an initial threshold of $p < .005$ are shown. Only clusters with peak activation within one of the volumes of interest are displayed. Sample images are AM10HAS and AM10ANS from the Karolinska Directed Emotional Faces stimulus set (36). L, left; MNI, Montreal Neurological Institute; R, right.

during emotion regulation (incongruent > congruent) but found no evidence in this direction (see Supplement for more details on this analysis).

In sum, the results support the hypothesis that reduced aPFC activation is associated with increased subsequent cortisol stress responses. Moreover, aPFC activation predicted not only HPA axis stress reactivity but also stress-induced increases in α -amylase and negative affect. Finally, the cortisol stress responsiveness was predicted by frontal emotion control to a larger extent in female subjects than in male subjects and was correlated to trait anxiety in female subjects.

DISCUSSION

Reduced aPFC activation during the regulation of social-emotional behavior is predictive for responsivity toward acute social stress. Using an fMRI emotion regulation task and stress induction procedure, we demonstrate that individuals who show less recruitment of the aPFC when they are required to suppress automatic social action tendencies also show a larger increase in salivary cortisol, salivary α -amylase, and negative affect after a subsequent formal social stress induction. Most critically, and at a more general level, our findings support the notion of a common ground underlying difficulty in controlling emotions and social stress sensitivity, which may play an important role in the development and maintenance of psychopathology.

Both reduced emotion regulation capabilities and altered functioning of the HPA axis function are hallmark characteristics of stress-related psychopathologies, including social

anxiety disorder and depression (2,5). For example, after similar social-emotional stress induction procedures, patients with social anxiety disorder showed an increase of the acute cortisol response (8,9). Abnormalities in the processing and regulation of emotion is a common trait in psychiatric conditions (2) in which deficient PFC functioning plays a major role (15,53). Recent studies show that this relationship is relevant for the specific type of emotion regulation operationalized in this study—the control over impulsive social approach-avoidance behavior. For instance, performance of the approach-avoidance task is marked by neurobehavioral alterations in social anxiety disorder, borderline personality disorder, and psychopathy (8,51,54). To our knowledge, this is the first study to show that the neural correlate of control over this type of clinically relevant social behavior can serve as a biomarker for stress responsiveness.

Our findings are in line with previous work showing a negative association between prefrontal activation and cortisol responses after stress (19), which has recently been replicated in patients with depression (20). However, because frontal activation in these studies was measured during the stress response, it is unclear whether this relationship reflects successful regulation of the social-emotional events that trigger the stress response, is part of a negative feedback mechanism prompted by the stress response itself, or is a combination of both. This was different for a study by Taylor *et al.* (55), who tested stress responsivity and threat regulation in separate sessions. Although they found indications for involvement of the ventrolateral PFC (adjacent to the aPFC), results were inconclusive, pointing at both an indirect negative relationship

and a positive relationship with cortisol increase. In the current study, we were able to link increased stress responsiveness to decreased activation in the aPFC, a region known to be involved in social-emotion control. This evolutionary relatively new region is implicated in abstract reasoning, counterfactual decision making, and relational thinking (56,57), but recent meta-analyses also underline the relevance of this area for emotion control, in particular flexibility in emotion control strategies (22,58,59). This fits with the notion that control over social-emotional behavior involves the implementation of more abstract goals while controlling immediate automatic responses. The aPFC appears to play a crucial role in this by influencing downstream activity in the amygdala (25,46). Our results indicate that prefrontal regulation of social-emotional cues may play an important role in the process underlying the stress response. Given that both short- and long-term stress impairs PFC functioning (60), decreased PFC functioning during stress may be part of a self-containing downward spiral, which could be a crucial factor in psychopathology [see also Ming *et al.* (20)].

To our knowledge, this is the first study to systematically investigate social-emotional prefrontal functioning as a biomarker or predicting factor of social stress sensitivity in a well-powered sample of 283 participants. In that light, there are a few issues worth to consider. First of all, we found that the relationship between PFC activation and stress responsivity was stronger for female subjects than for male subjects. Particularly, the finding that cortisol responses were related to trait anxiety in female subjects makes it valuable to replicate this finding in a study with a more balanced gender distribution, also in light of the gender difference that we found in the cortisol response itself, which is in line with meta-analyses (43,61,62). Moreover, future assessment of additional testosterone stress responses would be valuable because testosterone levels differ greatly between the sexes and have been shown to interact with cortisol levels (63). Second, although aPFC activation was predictive of cortisol responsivity, we found no such effect for aPFC-amygdala connectivity. Future research using more focused (high-resolution) imaging techniques could further explore whether stress sensitivity is linked to differences in connectivity between the PFC and limbic regions during emotion regulation. Significantly, our exploratory analysis on a link between task-related amygdala activation and stress responsivity did not yield conclusive evidence (see Supplement), which is in line with literature indicating that fear, on the one hand, and social stress, on the other, seem to rely on distinct neural mechanisms (4,64). Third, our version of the task is optimized to detect individual differences at the neural level while keeping behavioral effects relatively stable across individuals (65). Future studies using an additional, parallel behavioral zooming task version, where the face grows larger in size when one pulls the joystick and decreases in size when one pushes the joystick, would enable further investigation of the mediating role of the brain in the relationship between hormones and behavior. Fourth, salivary α -amylase levels significantly increased after stress induction, but this elevation was not significantly stronger than the increase in the non-stress group. This may be related to the large within-group variability for this measure, which warrants a larger nonstress group (current $n = 25$). Fifth, because saliva was collected up

to 30 minutes after stress onset, cortisol recovery patterns could not be assessed in this study. Sixth, the study population consisted of students, and 80% of the students attended a police academy. Future studies with a more heterogeneous sample should be conducted to assess the generalizability of these findings. Lastly, it would be interesting for future studies to include a nonemotional task condition to test whether effects are specific to control over prepotent emotional actions or also other forms of prepotent responses.

To conclude, individuals who show less frontal activation during the regulation of social-emotional behavior also show a stronger increase in stress-related measures to subsequent actual social stress exposure. These findings contribute to the delineation of an endophenotype of behavioral reactions to social stress cues and eventually should help to develop new tools to identify individuals who are resilient or at risk for developing stress-related psychopathology.

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Netherlands Trial Registry: Police-in-Action: The Role of Automatic Defensive Responses in the Development of Posttraumatic Stress Symptoms; <https://www.trialregister.nl/trial/5989>; NTR6355.

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REFERENCES

1. Etkin A, Büchel C, Gross JJ (2015): The neural bases of emotion regulation. *Nat Rev Neurosci* 16:693–700.
2. Gross JJ, Jazaieri H (2014): Emotion, emotion regulation, and psychopathology: An affective science perspective. *Clin Psychol Sci* 2:387–401.
3. McEwen BS, Gianaros PJ (2010): Central role of the brain in stress and adaptation: Links to socioeconomic status, health, and disease. *Ann N Y Acad Sci* 1186:190–222.
4. Ganzel BL, Morris PA, Wethington E (2010): Allostasis and the human brain: Integrating models of stress from the social and life sciences. *Psychol Rev* 117:134–174.
5. De Kloet ER, Joëls M, Holsboer F (2005): Stress and the brain: From adaptation to disease. *Nat Rev Neurosci* 6:463–475.
6. McEwen BS (1998): Stress, adaptation, and disease: Allostasis and allostatic load. *Ann N Y Acad Sci* 840:33–44.
7. Ulrich-Lai YM, Herman JP (2009): Neural regulation of endocrine and autonomic stress responses. *Nat Rev Neurosci* 10:397–409.
8. Roelofs K, van Peer J, Berretty E, de Jong P, Spinhoven P, Elzinga BM (2009): Hypothalamus-pituitary-adrenal axis hyperresponsiveness is

- associated with increased social avoidance behavior in social phobia. *Biol Psychiatry* 65:336–343.
9. Condren RM, O'Neill A, Ryan MCM, Barrett P, Thakore JH (2002): HPA axis response to a psychological stressor in generalised social phobia. *Psychoneuroendocrinology* 27:693–703.
10. Elzinga BM, Schmahl CG, Vermetten E, Van Dyck R, Bremner JD (2003): Higher cortisol levels following exposure to traumatic reminders in abuse-related PTSD. *Neuropsychopharmacology* 28:1656–1665.
11. Heim C, Newport DJ, Mletzko T, Miller AH, Nemeroff CB (2008): The link between childhood trauma and depression: Insights from HPA axis studies in humans. *Psychoneuroendocrinology* 33:693–710.
12. Olf M, van Zuiden M (2017): Neuroendocrine and neuroimmune markers in PTSD: Pre-, peri- and post-trauma glucocorticoid and inflammatory dysregulation. *Curr Opin Psychol* 14:132–137.
13. Arnsten AFT (2009): Stress signalling pathways that impair prefrontal cortex structure and function. *Nat Rev Neurosci* 10:410–422.
14. Radley JJ, Rocher AB, Miller M, Janssen WGM, Liston C, Hof PR, *et al.* (2006): Repeated stress induces dendritic spine loss in the rat medial prefrontal cortex. *Cereb Cortex* 16:313–320.
15. Beck AT (2008): The evolution of the cognitive model of depression and its neurobiological correlates. *Am J Psychiatry* 165:969–977.
16. Martin E, Ressler K, Binder E, Nemeroff C (2009): The neurobiology of anxiety disorders: Brain imaging, genetics, and psychoneuroendocrinology. *Psychiatr Clin North Am* 32:549–575.
17. Diorio D, Viau V, Meaney M (1993): The role of the medial prefrontal cortex (cingulate gyrus) in the regulation of hypothalamic-pituitary-adrenal responses to stress. *J Neurosci* 13:3839–3847.
18. Herman JP, Cullinan WE (1997): Neurocircuitry of stress: Central control of the hypothalamo-pituitary-adrenocortical axis. *Trends Neurosci* 20:78–84.
19. Kern S, Oakes TR, Stone CK, McAuliff EM, Kirschbaum C, Davidson RJ (2008): Glucose metabolic changes in the prefrontal cortex are associated with HPA axis response to a psychosocial stressor. *Psychoneuroendocrinology* 33:517–529.
20. Ming Q, Zhong X, Zhang X, Pu W, Dong D, Jiang Y, *et al.* (2017): State-independent and dependent neural responses to psychosocial stress in current and remitted depression. *Am J Psychiatry* 174:971–979.
21. Insel TR (2014): The NIMH Research Domain Criteria (RDoC) Project: Precision medicine for psychiatry. *Phys Rev B* 171:395–397.
22. Koch SBJ, Mars RB, Toni I, Roelofs K (2018): Emotional control, reappraised. *Neurosci Biobehav Rev* 95:528–534.
23. Bramson B, Jensen O, Toni I, Roelofs K (2018): Cortical oscillatory mechanisms supporting the control of human social-emotional actions. *J Neurosci* 38:5739–5749.
24. Roelofs K, Minelli A, Mars RB, van Peer J, Toni I (2009): On the neural control of social emotional behavior. *Soc Cogn Affect Neurosci* 4:50–58.
25. Volman I, Roelofs K, Koch S, Verhagen L, Toni I (2011): Anterior prefrontal cortex inhibition impairs control over social emotional actions. *Curr Biol* 21:1766–1770.
26. Radke S, Volman I, Mehta P, van Son V, Enter D, Sanfey A, *et al.* (2015): Testosterone biases the amygdala toward social threat approach. *Sci Adv* 1:e1400074.
27. Rohleder N, Nater UM, Wolf JM, Ehler U, Kirschbaum C (2004): Psychosocial stress-induced activation of salivary alpha-amylase: An indicator of sympathetic activity? *Ann N Y Acad Sci* 1032:258–263.
28. Tabachnik BG, Fidell LS (2001): *Using Multivariate Statistics*, 5th ed. Boston: Pearson.
29. Koch SBJ, Klumpers F, Zhang W, Hashemi MM, Kaldewaij R, van Ast V, *et al.* (2017): The role of automatic defensive responses in the development of posttraumatic stress symptoms in police recruits: Protocol of a prospective study. *Eur J Psychotraumatol* 8:1412226.
30. Watson D, Clark LA, Tellegen A (1988): Development and validation of brief measures of positive and negative affect: The PANAS scales. *J Pers Soc Psychol* 54:1063–1070.
31. Miller R, Stalder T, Jarczok M, Almeida DM, Badrick E, Bartels M, *et al.* (2016): The CIRCORT database: Reference ranges and seasonal changes in diurnal salivary cortisol derived from a meta-dataset comprised of 15 field studies. *Psychoneuroendocrinology* 73:16–23.
32. Chen M, Bargh JA (1999): Consequences of automatic evaluation: Immediate behavioral predispositions to approach or avoid the stimulus. *Pers Soc Psychol Bull* 25:215–224.
33. Volman I, Toni I, Verhagen L, Roelofs K (2011): Endogenous testosterone modulates prefrontal-amygdala connectivity during social emotional behavior. *Cereb Cortex* 21:2282–2290.
34. Ekman P, Friesen W (1975): *Pictures of Facial Affect*. Palo Alto, CA: Consulting Psychologists Press.
35. Matsumoto D, Ekman P (1988): *Japanese and Caucasian Facial Expressions of Emotion (JACFEE)*. San Francisco: Intercultural and Emotion Research Laboratory.
36. Lundqvist D, Flykt A, Ohman A (1998): *The Karolinska Directed Emotional Faces (KDEF) [CD ROM]*. Stockholm, Sweden: Department of Clinical Neuroscience, Psychology Section, Karolinska Institutet.
37. Martinez A, Benavente R (1998): *The AR face database*. CVC Technical Report No. 24. Barcelona, Spain: Centre de Visioper Computador, Universitat Autònoma de Barcelona.
38. Tyborska A, Volman I, Smeekens S, Toni I, Roelofs K (2016): Testosterone during puberty shifts emotional control from pulvinar to anterior prefrontal cortex. *J Neurosci* 36:6156–6164.
39. Luo Y, Fernández G, Hermans E, Vogel S, Zhang Y, Li H, Klumpers F (2018): How acute stress may enhance subsequent memory for threat stimuli outside the focus of attention: DLPFC-amygdala decoupling. *NeuroImage* 171:311–322.
40. Schwabe L, Haddad L, Schachinger H (2008): HPA axis activation by a socially evaluated cold-pressor test. *Psychoneuroendocrinology* 33:890–895.
41. Vogel S, Klumpers F, Kroes MCW, Oplaat KT, Krugers HJ, Oitzl MS, *et al.* (2015): A stress-induced shift from trace to delay conditioning depends on the mineralocorticoid receptor. *Biol Psychiatry* 78:830–839.
42. Duchesne A, Tessera E, Dedovic K, Engert V, Pruessner JC (2012): Effects of panel sex composition on the physiological stress responses to psychosocial stress in healthy young men and women. *Biol Psychol* 89:99–106.
43. Kudielka BM, Kirschbaum C (2005): Sex differences in HPA axis responses to stress: A review. *Biol Psychol* 69:113–132.
44. Lund TE, Nørgaard MD, Rostrup E, Rowe JB, Paulson OB (2005): Motion or activity: Their role in intra- and inter-subject variation in fMRI. *NeuroImage* 26:960–964.
45. Verhagen L, Grol MJ, Dijkerman HC, Toni I (2006): Studying visually-guided reach-to-grasp movements in an MR-environment. *NeuroImage* 31:S45.
46. Volman I, Verhagen L, den Ouden HEM, Fernández G, Rijpkema M, Franke B, *et al.* (2013): Reduced serotonin transporter availability decreases prefrontal control of the amygdala. *J Neurosci* 33:8974–8979.
47. Neubert FX, Mars RB, Thomas AG, Sallet J, Rushworth MFS (2014): Comparison of human ventral frontal cortex areas for cognitive control and language with areas in monkey frontal cortex. *Neuron* 81:700–713.
48. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, *et al.* (2002): Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage* 15:273–289.
49. Rottevel M, Phaf RH (2004): Automatic affective evaluation does not automatically predispose for arm flexion and extension. *Emotion* 4:156–172.
50. Radke S, Roelofs K, de Bruijn ERA (2013): Acting on anger: Social anxiety modulates approach-avoidance tendencies after oxytocin administration. *Psychol Sci* 24:1573–1578.
51. Bertsch K, Roelofs K, Roch PJ, Ma B, Hensel S, Herpertz SC, Volman I (2018): Neural correlates of emotional action control in anger-prone women with borderline personality disorder. *J Psychiatry Neurosci* 43:161–170.
52. Dickerson SS, Kemeny ME (2004): Acute stressors and cortisol responses: A theoretical integration and synthesis of laboratory research. *Psychol Bull* 130:355–391.
53. Phillips ML, Ladouceur CD, Drevets WC (2008): A neural model of voluntary and automatic emotion regulation: Implications for

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- understanding the pathophysiology and neurodevelopment of bipolar disorder. *Mol Psychiatry* 13:833–857.
54. Volman I, von Borries AKL, Bulten BH, Verkes RJ, Toni I, Roelofs K (2016): Testosterone modulates altered prefrontal control of emotional actions in psychopathic offenders. *eNeuro* Feb 8;3(1).
 55. Taylor SE, Burklund LJ, Eisenberger NI, Lehman BJ, Hilmert CJ, Lieberman MD (2008): Neural bases of moderation of cortisol stress responses by psychosocial resources. *J Pers Soc Psychol* 95:197–211.
 56. Vendetti MS, Bunge SA (2014): Evolutionary and developmental changes in the lateral frontoparietal network: A little goes a long way for higher-level cognition. *Neuron* 84:906–917.
 57. Mansouri FA, Koechlin E, Rosa MGP, Buckley MJ (2017): Managing competing goals—A key role for the frontopolar cortex. *Nat Rev Neurosci* 18:645–657.
 58. Kalisch R (2009): The functional neuroanatomy of reappraisal: Time matters. *Neurosci Biobehav Rev* 33:1215–1226.
 59. Morawetz C, Bode S, Derntl B, Heekeren HR (2017): The effect of strategies, goals and stimulus material on the neural mechanisms of emotion regulation: A meta-analysis of fMRI studies. *Neurosci Biobehav Rev* 72:111–128.
 60. Arnsten AFT, Raskind MA, Taylor FB, Connor DF (2015): The effects of stress exposure on prefrontal cortex: Translating basic research into successful treatments for post-traumatic stress disorder. *Neurobiol Stress* 1:89–99.
 61. Kajantie E, Phillips DIW (2006): The effects of sex and hormonal status on the physiological response to acute psychosocial stress. *Psychoneuroendocrinology* 31:151–178.
 62. Liu JJW, Ein N, Peck K, Huang V, Pruessner JC, Vickers K (2017): Sex differences in salivary cortisol reactivity to the Trier Social Stress Test (TSST): A meta-analysis. *Psychoneuroendocrinology* 82:26–37.
 63. Mehta PH, Jones AC, Josephs RA (2008): The social endocrinology of dominance: Basal testosterone predicts cortisol changes and behavior following victory and defeat. *J Pers Soc Psychol* 94:1078–1093.
 64. Pruessner JC, Dedovic K, Khalili-Mahani N, Engert V, Pruessner M, Buss C, *et al.* (2008): Deactivation of the limbic system during acute psychosocial stress: Evidence from positron emission tomography and functional magnetic resonance imaging studies. *Biol Psychiatry* 63:234–240.
 65. Price CJ, Friston KJ (1999): Scanning patients with tasks they can perform. *Hum Brain Mapp* 8:102–108.