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Medial prefrontal cortex damage affects physiological and psychological stress responses differently in men and women

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Summary The ability to produce appropriate physiological and psychological responses to stressful situations depends on accurate recognition and appraisal of such situations. Such ability is also important for proper emotion regulation. A number of studies have suggested that the medial prefrontal cortex (mPFC) plays a significant role in emotion regulation, as well as in the control of physiological endpoints of emotion regulation such as the hypothalamic—pituitary—adrenal (HPA) axis and autonomic nervous system (ANS). Further, recent work has suggested that men and women may differ in these mechanisms of neural control of emotion regulation. Here, we examined the role of the human mPFC in self-report, ANS, and HPA stress reactivity by testing a group of participants with damage to this region (9 women and 9 men), a brain damaged comparison group (6 women and 6 men), and healthy comparison participants (27 women and 27 men) on an orthostatic challenge and the Trier Social Stress Test (TSST). The mPFC participants showed heightened self-reported stress in response to the TSST. In women, mPFC damage led to an *increased* cortisol response to the TSST. By contrast, in men, greater volume of mPFC damage was correlated with a *decreased* cortisol response. Finally, men with mPFC damage showed altered autonomic control of the heart (higher heart rate and lower high frequency heart rate variability) during an orthostatic challenge. These findings support the idea that the mPFC is involved in the regulation of physiological and psychological responses to stress and that this regulation may differ between men and women.

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1. Introduction

A wealth of research has focused on understanding the neural regulation of the stress response (McEwen, 2000; Herman et al., 2003; Lovallo, 2005). This work has highlighted the importance of the hypothalamus and pituitary gland as key controllers of stress reactivity, but many forebrain areas such as the medial prefrontal cortex (mPFC; Diorio et al., 1993; Sullivan and Gratton, 1999; Maier et al., 2006), amygdala (Feldman et al., 1995; Jankord and Herman, 2008) and hippocampus (HC; Sapolsky et al., 1984; Herman et al., 2003) are also involved. The role that these structures play in determining the stress-inducing nature of a stimulus and enacting a stress response has been addressed mostly with animal models. More recent work has focused on these issues in humans, using either the lesion method (Buchanan et al., 2004, 2009; Wolf et al., 2005) or functional neuroimaging (Wang et al., 2005; Urry et al., 2006; Kern et al., 2008; Pruessner et al., 2008). This work has generally provided evidence supporting the roles of the mPFC, hippocampus, and amygdala in controlling the stress response in humans.

The mPFC is involved in the control of many aspects of stress and emotion. Humans with bilateral damage to this region show deficits in the regulation of emotion in laboratory tasks as well as in their daily lives (Bechara et al., 1994; Anderson et al., 2006). The pattern of disturbed emotion regulation in these individuals (sometimes termed 'frontal disinhibition syndrome') includes flattened affect as well as impulsivity, risk taking, and emotional outbursts that are incommensurate with the provocation (Barrash et al., 2000; Berlin et al., 2004; Floden et al., 2008). Although electrodermal responses after mPFC damage tend to be reduced in response to emotional stimuli (Tranel and Damasio, 1994), some studies have reported pronounced cardiovascular activation in mPFC lesion patients (Critchley et al., 2003; Hilz et al., 2006). Critchley et al. (2003) demonstrated increased heart rate and decreased heart rate variability to mental stress in patients with mPFC (specifically anterior cingulate) damage, suggesting reduced inhibitory control of the heart after mPFC damage. Further, neuroimaging studies have suggested that the mPFC exerts inhibitory control over autonomic and endocrine output (Wang et al., 2005; Ahs et al., 2006; Urry et al., 2006; Kern et al., 2008; Pruessner et al., 2008; Lane et al., 2009). Damage to this region, then, could result in a disinhibition of psychological and physiological responses to stress.

The mPFC is not a unitary structure; many studies have documented different functions for the left versus right mPFC and of the ventral versus dorsal regions. Rats with lesions to the right mPFC show decreased stress reactivity, while left-sided damage does not affect the stress response (Sullivan and Gratton, 1999). In work with humans, Tranel et al. (2002) have shown that patients with damage to the right ventral mPFC show a pattern of disturbed social and emotional behavior akin to that previously described for patients with bilateral damage to this region, whereas patients with left-sided damage do not show this pattern. More recent work suggests that this asymmetric pattern of disturbance following unilateral lesions is different between the sexes, such that men with right-sided, but not left-sided damage and women with left-sided, but not right-sided damage show this altered social and emotional behavior, following damage to the mPFC (Tranel et al., 2005) or the amygdala (Tranel and Bechara, 2009). A large body of research has documented sex differences in a host of neural functions (see Cahill, 2005). This work has documented sex differences in neural activity during cognitive tasks such as memory (Andreano and Cahill, 2009) and naming (Grabowski et al., 2003) as well as in more "emotional" tasks such as memory for emotion (Buchanan and Tranel, 2008) and in the cognitive control of emotional processing (Koch et al., 2007; McRae et al., 2008). These findings suggest that reactions to stress may depend on different neural structures for men and women.

Psychological stress is unique in that the stressful nature of the situation is determined by its perceived threat value, which may be unrelated to the actual threat of a situation (Lazarus and Folkman, 1984). For example, some people may perceive the act of giving a speech to be terrifying, while others may perceive the act to be a neutral, or even a positive situation. This model of stress proposes that the interaction between the stressor and an individual's appraisal processes result in the stress response. These appraisals are processed by neural areas including the mPFC (Rudebeck et al., 2008), which in turn activate hypothalamic and brain stem regions responsible for the initiation of the physiological stress response (Öngür et al., 1998).

Patients with mPFC damage have difficulty interpreting social and emotional cues (Hornak et al., 1996; Beer et al., 2003; Mah et al., 2004; Heberlein et al., 2008). Damage to the mPFC may therefore impair the appreciation of the stressful nature of a situation, leading to inappropriate psychological and physiological reactivity to social stress, which could be manifested through either hypo- or hyperreactivity. A number of investigators have noted this frontal disinhibition pattern in individuals with damage to the mPFC. Jarvie (1954) gave several examples of disinhibitory behavior in such patients. One of these patients, who had bilateral damage to the frontal poles, described, in a flat, matter-of-fact manner "... how the girl whom he had intended marrying had become pregnant by another man..." In spite of this blunted affect when describing a presumably emotional event, in his daily life the patient "... admitted to being very irritable at times, losing his temper, and on occasions smashing some articles at home." The patient's volatility was corroborated by his mother, who described him as "... bad-tempered, irritable, and frightening in his aggressiveness." (see also Koenigs and Tranel, 2007 for other examples of such a discrepancy between baseline blunted affect coupled with emotional outbursts).

Psychological stress may present a real challenge for individuals with mPFC damage because the stressful nature of a situation depends on one's appraisal of the situation. If these individuals have difficulty interpreting the stressful nature of a situation that others may describe as stressful, they may produce an abnormal response to the situation. This study had three objectives: The first objective was to examine the stress responses of participants with mPFC lesions. To do this, we measured salivary cortisol, heart rate, heart rate variability, and subjective affective responses to an orthostatic challenge and the Trier Social Stress Test (TSST). The orthostatic challenge was designed to assess basic autonomic function and the Trier Social Stress Test (TSST) to assess reactivity to psychological stress. We anticipated that, given

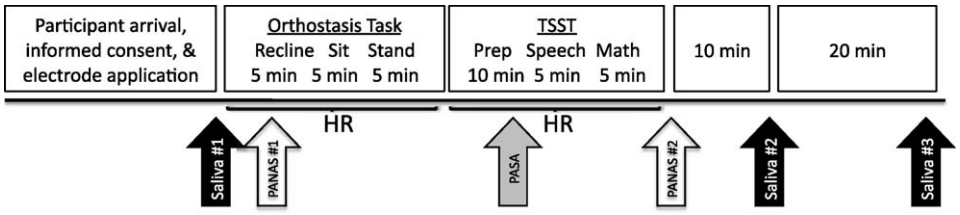

Figure 1 Experimental protocol and timeline. Heart rate (HR) was collected throughout the orthostasis task and TSST. PANAS = Positive Affect/Negative Affect Schedule, PASA = Primary Appraisal/Secondary Appraisal scale, HR = heart rate.

the pattern of disinhibition shown by mPFC lesion patients, they would show abnormal reactivity to stress compared to comparison groups. Given the altered emotional regulation pattern shown by these patients, we were agnostic about the direction of their response to stress. The second objective was to address whether the laterality of mPFC lesions was associated with stress reactivity. To address this issue, we compared stress reactivity between those with left- and right-sided damage and we examined the extent of damage to the right versus left mPFC in each participant using analysis of lesion volumes of the mPFC from magnetic resonance imaging (MRI) or computed tomography (CT). Based on prior work, we predicted that right-sided damage would be associated with greater stress reactivity. The third objective was to examine the role that sex may play in the relationship between the mPFC and stress. These analyses were exploratory in nature given the small sample size to detect both sex and laterality effects.

2. Materials and methods

2.1. Participants

Eighteen participants with brain damage including the mPFC (see Fig. 1 for lesion overlap), 12 participants with brain damage outside the PFC, and 54 healthy volunteers participated in the study (see Table 1 for participant characteristics). Causes of damage in the mPFC group were: seven with meningioma resections, five with subarachnoid hemorrhage after anterior communicating artery aneurysm rupture, two with frontal infarctions, two with trauma, one subarachnoid cyst removal, and one arteriovenous malformation resection. The brain damaged comparison (BDC) participants had damage due to stroke. This group included three participants with lateral temporal lobe damage, five with parietal lobe damage, and four with occipital lobe damage. Comparison participants were matched to the brain damaged participant groups on age and sex distribution (see Table 1). All brain injured participants were selected from the Patient Registry of the Division of Cognitive Neuroscience at the University of Iowa, under the auspices of which they have undergone extensive neuropsychological and neuroanatomical assessments. None of the participants were taking medications that may affect cortisol levels (e.g., any steroid-based drug such as prednisone or estrogen/progesterone hormone replacement or oral contraceptives).

2.2. Neuroanatomical data

Magnetic resonance images were obtained from 12 of the mPFC participants in a 1.5 T General Electric scanner, while CT scans were obtained for 6 participants who were unable to undergo an MRI scan. The scanning protocol used in this study was identical to that used in previous work from our laboratory (Allen et al., 2002; Buchanan et al., 2004). The MAP-3 technique (Frank et al., 1997) was utilized to allow for analysis of the placement of lesions across the 18 mPFC participants. This technique involves: (1) visualizing MR/CT slices of a lesioned brain and a reference brain reconstructed in three dimensions using Brainvox software (Frank et al., 1997), (2) creating a match between the two brains so that both are in the same orientation, and (3) using anatomical landmarks to manually warp the lesion contours onto the reference brain, which allows one to represent lesions from multiple subjects in a common space. Using this technique, the volume of gray and white matter damage within the entire PFC region was calculated within each hemisphere for each of the 18 mPFC participants.

For the current study, only the ROIs from the medial surface of the PFC and those lateral regions bordering the medial surface of the PFC were included in correlation analyses. These include the following ROIs from the medial surface: anterior and subgenual cingulate gyrus, anteromedial and ventromedial superior frontal gyrus, frontal pole, medial orbitofrontal gyrus, and gyrus rectus. The following ROIs were included from the lateral surface: anterolateral superior frontal gyrus, anterior middle frontal gyrus, and the lateral orbital gyrus. The volumes of these regions were combined to form total lesion volume measures for each participant of the right, left, and bilateral PFC (see

Table 1 Demographics. Mean age and education in years ± standard deviation.

Participant	Mean age	Mean education	Sex	Side of lesion
mPFC group (N = 18)	53.6 ± 13.9	13.8 ± 1.9	9M/9F	11B/3L/4R
Brain damaged comparison (N = 12)	56.3 ± 10.4	13.9 ± 3.1	6M/6F	2B/7L/3R
Healthy comparison participants (N = 54)	50.2 ± 10.7	16.0 ± 2.5	27M/27F	—

Table 2 Mean (±S.E.M.) volume of mPFC damage for the left and right hemispheres and total bilateral volume for females and males in cubic mm (greater numbers signify greater volume of damage). Note that data from all participants with mPFC damage, regardless of laterality, are included here.

Sex	Laterality of damage	Left volume	Right volume	Bilateral volume
Female	6B/1L/2R	14,106 ± 4058	18,150 ± 5213	32,256 ± 6457
Male	5B/2L/2R	17,060 ± 6475	22,470 ± 7304	39,530 ± 7794

Table 2 for neuroanatomical data; note that in the table, greater numbers signify greater volume of damage).

2.3. Protocol

Fig. 2 depicts the experimental protocol and timeline of events. Participants completed an informed consent document approved by the University of Iowa IRB. Participants completed an orthostatic challenge and then the Trier Social Stress Test (TSST). The orthostatic challenge consists of measuring autonomic function while reclining, sitting, and standing, each for a 5 min interval. This protocol has been used previously to assess reflex control of cardiovascular function (Weipert et al., 1987; Panknin et al., 2002). The TSST consists of an anticipation period (10 min) and a test period (10 min) during which participants deliver a speech and perform mental arithmetic in front of an ''audience'' of experimenters. Participants were randomly assigned to one of two scenarios on which to base their speech: a mock job interview ($N = 40$) or a mock accusation of shoplifting ($N = 44$). Responses to the two scenarios did not differ across the whole sample ($F < 1$, $p > 0.3$), nor were there differences in responses to the two scenarios within the participant groups (no Group × Scenario interaction: $F < 1$, $p > 0.5$). After preparation, the participant was escorted to a conference room where the speech and math portion of the task were completed while standing. Two experimenters were present during the TSST and the participant was videotaped throughout.

Saliva samples were obtained using a commercially available collection device (Salivette®, Sarstedt, Rommelsdorf, Germany). Samples were taken at three time points: Sample #1 was taken 15 min after arrival in the laboratory (35 min elapsed between Samples 1 and 2), Sample #2 was taken at 10 min and Sample #3 was taken at 30 min after the end of the TSST. Samples were stored at −20 °C until assayed. Salivary cortisol was measured with a commercial immunoassay kit (CLIA, IBL Hamburg, Germany). Intraassay and interassay coefficients of variation were less than 10%. The cortisol area under the curve with respect to increase (AUC) was computed for each individual for use in correlation analyses (Pruessner et al., 2003).

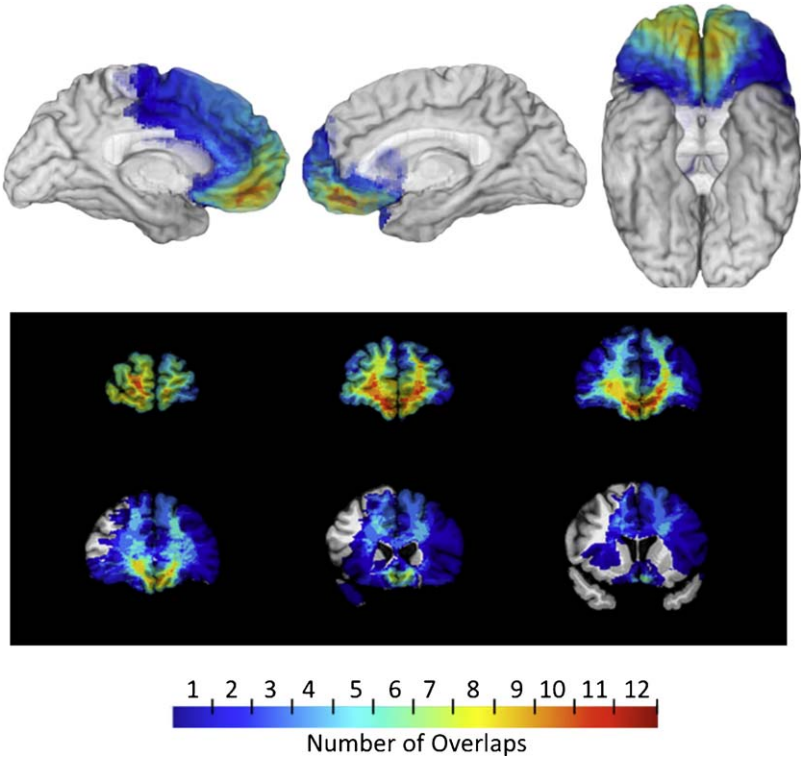

Figure 2 Lesion overlap of mPFC participants. Lesions of 18 participants with mPFC damage displayed in mesial (left and right hemispheres separately) and ventral views and coronal slices below. The color bar indicates the number of overlapping lesions at each voxel.

Valid electrocardiogram (ECG) data were recorded from 14 (8 women) mPFC, 12 (6 women) BDC, and 37 (16 women) healthy comparison participants. Appropriate degrees of freedom are reported for each analysis of these data. The ECG was measured throughout the orthostatic challenge as well as during the preparation and performance phases of the TSST from two leads: one placed on the right side of the neck and the other on the left side of the torso 2 cm below the rib cage. Beat-to-beat heart rate variability data were averaged into 5 min intervals for each position in the orthostatic challenge and for 10 min intervals for the preparation and presentation of the TSST. Spectral analysis of the heart rate variability using autoregressive techniques were used to obtain low frequency (LF, 0.04—0.15 Hz) and high frequency (HF, 0.15—0.40 Hz) components. The LF component is thought to reflect sympathetic influence over heart rate, while the HF component is more associated with parasympathetic control (Berntson et al., 1997; Thayer et al., 2009). Further, the ratio between the LF and HF components was calculated as a relative measure of sympathetic versus parasympathetic control over the heart. These frequency components were logarithmically transformed to correct for violation of normality.

Subjective responses to the TSSTwere collected using two scales: the Positive Affect/Negative Affect Schedule (PANAS; Watson et al., 1988) and the Primary Appraisal/Secondary Appraisal scale (PASA; Gaab et al., 2005). The PANAS was collected at two time points: 15 min after arrival in the laboratory and immediately after completion of the TSST. Difference scores for both positive and negative affect scales were created by subtracting the values from the first from those obtained from the second administration of the PANAS. The PASA was administered between the preparation and presentation phases of the TSST. It contains four subscales that assess different components of the psychological appraisal of a stressor and an individual's ability to respond to it: threat, challenge, self-concept of own abilities, and control expectancy. Responses on this scale are associated with cortisol responses to stress (Gaab et al., 2005).

2.4. Data analysis

Cortisol data were transformed into area under the curve with respect to increase (AUC; Pruessner et al., 2003) in order to reduce the total number of observations while preserving the multiple observations that were collected. These data were analyzed using a 3 Group (mPFC, BDC, healthy comparison) × 2 Sex ANOVA. Heart rate and heart rate variability were analyzed separately for the orthostasis task and the TSST. For the orthostasis task, data were analyzed using a 3 Group (mPFC, BDC, healthy comparison) × 2 Sex × 3 Time Period (Recline, Sit, Stand) ANOVA with repeated measures on the Time factor. For the TSST, data were analyzed using a 3 Group (mPFC, BDC, healthy comparison) × 2 Sex × 2 Time Period (TSST-preparation, TSST-performance) ANOVA with repeated measures on the Time factor. Subjective reports were analyzed using a Group × Sex MANOVA. Sex was included as a factor in all analyses, because men tend to show greater laboratory stress responses than women (Kudielka and Kirschbaum, 2005), and because the overall objectives of the study included investigation of this factor. Measures of effect size are reported using partial eta-squared (η^2). Pearson's r correlation coefficients are reported for analyses of the relationships between neuroanatomical volumes and stress indices.

3. Results

The basic findings of the study indicate that damage to the mPFC does alter subjective, hormonal, and autonomic stress reactivity (addressing objective 1 outlined in Section 1). Further, laterality of lesion does not seem to influence this reactivity (ala objective 2). Finally, these effects are different between men and women (ala objective 3). Specific results are outlined below with reference to the overall objectives.

3.1. Cortisol responses

Fig. 3 shows mean cortisol area under the curve for each group separated by sex in response to the TSST; Table 3 shows cortisol values across all time periods for each group separated by sex. There was no difference in cortisol response among the groups ($F < 1$, $p > 0.5$), but a significant effect of sex, with men showing greater responses than women ($F(1,78) = 6.0$, $p < 0.05$, partial eta-squared = 0.07) and a group by sex interaction, $F(2,78) = 3.3$, $p < 0.05$, partial eta-squared = 0.08. Men in all three of the groups showed significant cortisol increases that did not differ among the groups ($ps > 0.2$). Among women, only those with mPFC damage showed an increase, which was significantly larger than the NC group ($p < 0.01$; the mPFC group was not significantly different from the BDC group, however, $p > 0.15$). These findings fit with the often reported sex differences in free cortisol response (Kudielka and Kirschbaum, 2005) and suggest a disinhibitory effect of damage to the mPFC in women, in that a task that did not produce a

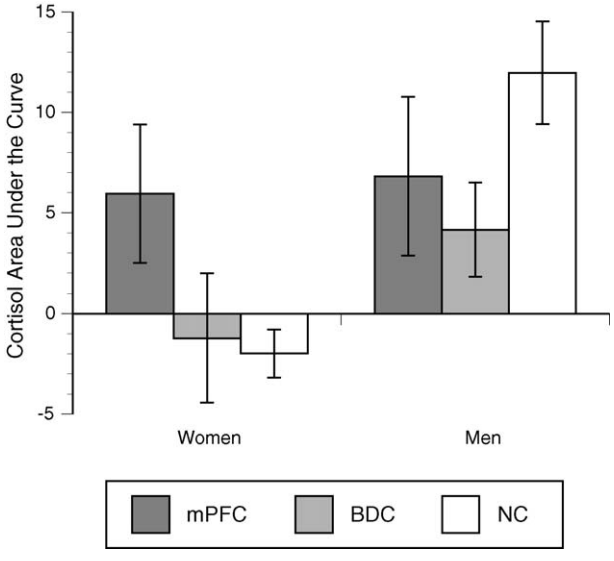

Figure 3 Cortisol levels across groups. Data show mean (±S.E.M.) of cortisol area under the curve from before to after the Trier Social Stress Test (TSST) in the medial prefrontal group (mPFC), the brain damage comparison group (BDC), and normal comparison group (NC), separated by sex.

Table 3 Mean (±S.E.M.) cortisol levels across sex, group, and time.

Sex	Group	Pre-TSST	TSST + 10	TSST + 30
Female	mPFC	6.9 (0.7)	11.6 (2.6)	9.5 (2.0)
	BDC	12.0 (1.7)	12.0 (3.0)	9.5 (1.7)
	Healthy comparison	8.4 (0.8)	7.4 (0.8)	6.6 (0.7)
Male	mPFC	10.2 (1.6)	15.4 (3.1)	13.5 (2.7)
	BDC	8.2 (1.3)	12.0 (1.5)	9.1 (1.0)
	Healthy comparison	7.3 (0.8)	16.3 (1.9)	13.3 (1.6)

reliable cortisol response in women was successful in producing a response following mPFC lesion (see Kern et al., 2008). These findings address research objectives 1 and 3, demonstrating that mPFC damage does affect cortisol reactivity to the TSST and that this effect is moderated by the sex of the participant.

3.2. Heart rate responses

Fig. 4 shows mean heart rate for each group, separated by sex, during each phase of the orthostatic challenge and TSST preparation and presentation. During orthostasis, there was a pronounced effect of time across all groups ($F(2,52) = 51$, $p < 0.0001$, partial eta-squared = 0.66), additionally there was a significant Group × Sex × Time interaction ($F(4,104) = 2.9$, $p < 0.05$, partial eta-squared = 0.1). Post-hoc contrasts, separated by sex, indicate that this interaction was due primarily to a significant difference in the men's HR between the mPFC and comparison groups during the standing condition of the orthostatic challenge ($ps < 0.05$; see Fig. 4). These effects were not found for women ($ps > 0.5$). There was a trend toward a significant main effect of group ($F(2,53) = 2.9$, $p = 0.07$, partial eta-squared = 0.01), but no main effect of sex ($F(1,53) < 1$, $p > 0.7$, partial eta-squared = 0.002), nor was there a sex by group interaction ($F(2,53) = 1.7$, $p = 0.2$, partial eta-squared = 0.06).

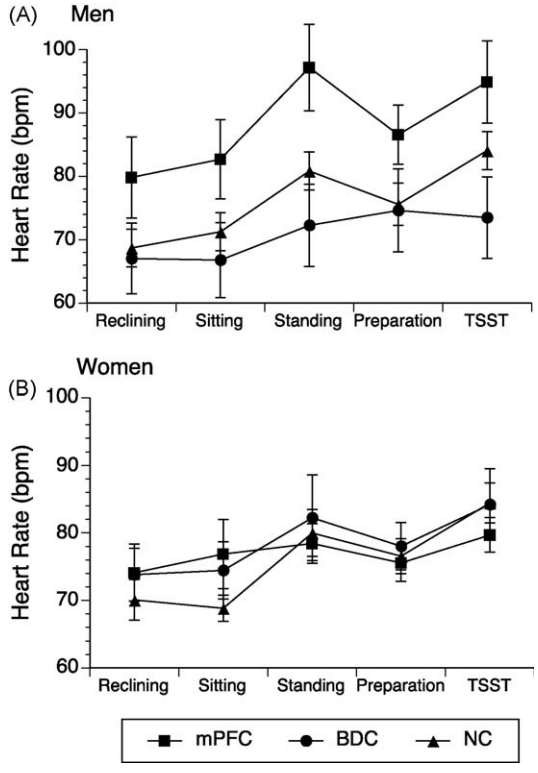

Figure 4 (A and B) Heart rate across groups and experiment, separated by sex. Data show mean (±S.E.M.) of heart rate during the reclining, sitting, and standing phases of the orthostatic challenge and during the preparation and presentation phases of the Trier Social Stress Test (TSST) in the medial prefrontal group (mPFC), the brain damage comparison group (BDC), and normal comparison group (NC). A: Men, B: Women.

From the preparation to presentation phase of the TSST, heart rate increased across all groups ($F(1,55) = 32$, $p < 0.0001$, partial eta-squared = 0.37). There were trends toward interactions between group and time ($F(2,55) = 2.8$, $p = 0.07$, partial eta-squared = 0.09) and among sex, group, and time ($F(2,55) = 2.6$, $p = 0.09$, partial eta-squared = 0.09). There were no main effects of group or sex, however.

3.3. Heart rate variability

To determine the underlying autonomic functions of the participant groups in response to orthostasis and the TSST, analyses were performed on low frequency (LF) and high frequency (HF) components of the beat-to-beat interval as well as on the ratio between the two components (LF/HF). Across both orthostasis and TSST, there were no significant effects for the LF component, so this variable will not be further discussed. Fig. 5 shows mean, log-transformed HF heart rate variability for each group, separated by sex, during each phase of the orthostatic challenge and TSST preparation and presentation.

During orthostasis, the participants showed significant differences in HF variability and the LF/HF ratio across time (main effect of time: $Fs(2,51) > 11$, $ps < 0.0001$, partial eta-squareds > 0.3; see Fig. 5 for presentation of HF data from the orthostasis task). Like the differences in HR, group differences in HF and LF/HF were most apparent in men between the mPFC and healthy comparison groups during the standing condition of the orthostatic challenge ($ps < 0.05$). There were no such effects among the women.

From the preparation phase to the presentation phase of the TSST, measures of HF variability and the HF/LF ratio were not significantly different across the factors of time, sex, or group ($ps > 0.2$; see Fig. 5 for presentation of HF data from the TSST). Generally, all participants showed similar patterns of activity within these variables from preparation to the presentation phase of the TSST.

These findings address research objectives 1 and 3, demonstrating that mPFC damage does affect autonomic

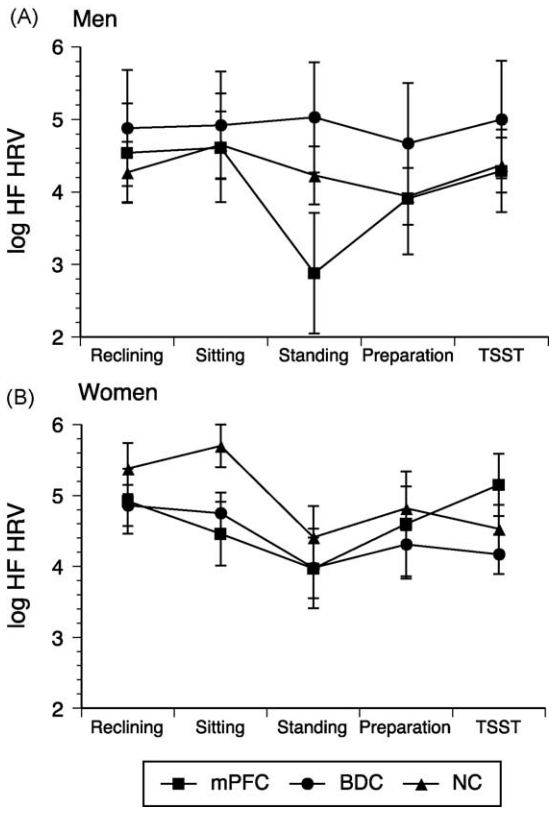

Figure 5 Log transformed high frequency heart rate variability across groups and experiment, separated by sex. Data show mean (±S.E.M.) of log transformed high frequency heart rate variability during the reclining, sitting, and standing phases of the orthostatic challenge and during the preparation and presentation phases of the Trier Social Stress Test (TSST) in the medial prefrontal group (mPFC), the brain damage comparison group (BDC), and normal comparison group (NC). A: Men; B: women.

reactivity, primarily to the orthostasis task and that this effect is moderated by the sex of the participant. These findings suggest that the autonomic differences between groups exist at baseline, and are exacerbated by postural challenges more than by the psychosocial challenge of the TSST.

3.4. Subjective responses

Measures of threat, challenge, self-concept of own abilities, and control expectancy from the PASA and prestress to poststress changes in positive and negative affect from the PANAS were subjected to a multivariate analysis of variance (MANOVA) with Group and Sex as factors. There was a main effect of Group, $F(12,138) = 5.1$, $p < 0.001$, partial eta-squared = 0.31 (see Table 4). Planned contrasts demonstrated that the mPFC group reported more threat and negative affect, lower self-concept of own abilities, and lower positive affect compared to the healthy comparison group ($ps < 0.05$). The BDC group did not differ from the mPFC or the healthy comparison group across any of these measures. There was no main effect of sex, nor was there a group by sex interaction ($Fs < 1.7$, $ps > 0.15$). These findings address the first research objective and demonstrate that participants with mPFC damage perceived the TSST as stressful and rated the task as even more negative than the comparison groups.

3.5. Associations between mPFC volume and stress measures

In order to examine potential sex differences in the laterality or sizes of mPFC lesions, the ratio of men and women with damage to the left, right, or bilateral mPFC was examined. Additionally, volumetric data from the mPFC lesions were compared across men and women. There were no significant sex differences in the number of participants with lesions affecting the right, left, or bilateral mPFC ($\chi^2 < 1$, $p > 0.8$; see Table 2), nor were there significant sex differences in the volumes of left, right, or bilateral mPFC ($ts(16) < 1.2$, $ps > 0.2$).

Lesion volumes from the mPFC were used to examine the associations among the volume of mPFC damage and cortisol, cardiac, and subjective stress responses. Participants with greater volume of mPFC damage showed lower cortisol AUC ($r = -0.48$, $p < 0.05$). Analyses conducted separately for men and women showed that this effect was driven by the association in men ($r = -0.86$, $p = 0.01$), while women showed no such association ($r = -0.02$, $p > 0.9$; see Fig. 6).

Research has suggested that the left versus right mPFC may exert differential control over the HPA axis (Sullivan and Gratton, 1999, 2002). In relation to the second research

Table 4 Affective responses to TSST. Entries show mean ± S.E.M.

Sex	Group	Change in positive affect	Change in negative affect	Threat	Challenge	Self-concept	Control expectancy
Female	mPFC	−4.7 (2.3)*	13.4 (2.2)*	3.4 (0.3)*	3.6 (0.2)	3.4 (0.3)*	4.2 (0.3)
	BDC	0.3 (2.2)	4.0 (2.3)	2.7 (0.4)	4.0 (0.2)	3.5 (0.4)	4.3 (0.3)
	Healthy comparison	−0.4 (1.2)	4.0 (0.8)	2.1 (0.2)	3.6 (0.2)	4.0 (0.2)	4.2 (0.2)
Male	mPFC	−4.1 (1.9)*	10.7 (2.4)*	2.6 (0.4)*	3.3 (0.4)	3.7 (0.2)*	4.4 (0.2)
	BDC	0.7 (3.5)	6.5 (4.2)	1.0 (0.4)	3.3 (0.7)	3.9 (0.4)	3.8 (0.3)
	Healthy comparison	0.4 (1.1)	2.4 (0.7)	2.2 (0.2)	3.7 (0.2)	4.1 (0.2)	4.3 (0.2)

* Significant difference from comparison participants using Bonferroni corrected multiple comparison procedure.

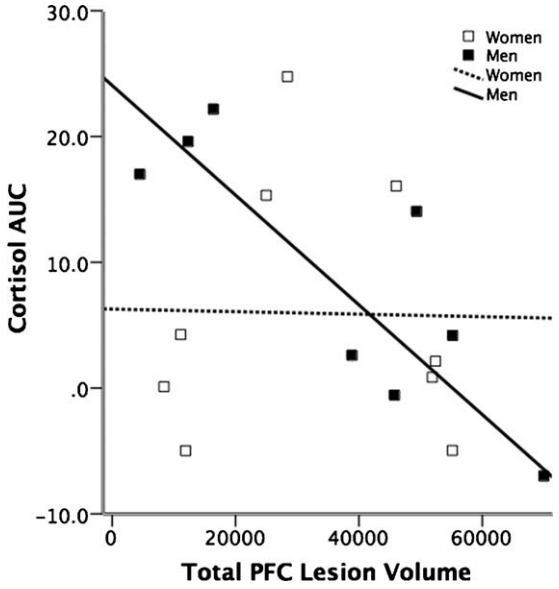

Figure 6 Association between total prefrontal lesion volume and area under the curve of cortisol response to the Trier Social Stress Test (TSST) across men and women.

objective outlined in Section 1, we examined the association between the volume of damage in the right and left PFC with cortisol AUC. Volume of damage within the left and right PFC in men was negatively associated with cortisol AUC, but did not reach statistical significance ($rs = -0.52$ and -0.46, respectively, $ps > 0.1$). Further, neither of these analyses was significant in women ($rs < |0.3|$).

Volume of mPFC damage was not significantly associated with HR responses to the TSST, defined as HR during the TSST minus HR during the sitting period of orthostasis ($r < 0.2$, $p > 0.5$).[1] Further, there were no significant associations between mPFC damage volume and any of the HRV measures ($rs < 0.4$, $ps > 0.15$).

There were no significant associations between volume of mPFC lesion and PA, NA, or PASA data ($rs < 0.33$) across the whole sample. When the analyses were run on men and women separately, however, the men showed a significant negative correlation between total mPFC lesion volume and self-concept of their abilities on the task ($r = -0.77$, $p < 0.05$), while women did not show such an association ($r = 0.4$, $p > 0.2$). There were no other sex-specific associations between lesion volume and subjective reports ($ps > 0.1$). These findings address objectives 2 and 3 by demonstrating that laterality of lesion was not associated with reactivity in this study, but that sex of the participant did affect the relationship between lesion volume and reactivity.

4. Discussion

The ability to recognize a situation as stressful and produce the appropriate psychological and physiological responses is necessary for adaptive behavior. Both over reactions and under reactions could lead to inappropriate psychological and physiological responses to stress. Results from this study show that damage to a region of the brain known to be necessary for the proper regulation of emotional reactivity leads to a disinhibited pattern of stress reactivity. Specifically, patients with damage to the mPFC show increased affective responses to stress, pronounced cortisol responses to the TSST and less inhibition of cardiovascular activity during the orthostatic challenge. One of the primary characteristics of patients with damage to the mPFC is affective volatility (Anderson et al., 2006). This volatility may be due to a more general disinhibitory effect of mPFC damage—that is, behavior and physiology normally kept in check through the actions of the mPFC are no longer inhibited following damage to this region. Alternative interpretations and caveats such as sex differences must be considered alongside this interpretation, however.

Male participants tended to show greater cortisol responses to the TSST than did women, an effect that was observed across participant groups, regardless of brain lesion status. Importantly, among the female participants, the only group to show a significant cortisol response was the women with mPFC damage, while women in the normal comparison and brain damage comparison groups did not show a cortisol response. Although women were generally less reactive than men to our stress manipulation, those women with mPFC damage nonetheless showed a significant cortisol response. These findings support the notion that the mPFC serves an inhibitory role over the HPA axis; in response to a stressor that did not produce a significant cortisol response in two matched comparison groups of women, those women with mPFC damage did show a response to the task. By contrast, in men, greater mPFC lesion volume was associated with less cortisol response.

In contrast to these sex-specific effects of mPFC lesions on cortisol reactivity, the opposite sex-specific pattern was observed for heart rate and heart rate variability: male mPFC participants showed higher HR and lower HRV especially during standing. These findings support the idea of differential control over hormonal versus autonomic stress reactivity. Previous work has demonstrated a dissociation between the autonomic and cortisol responses to the TSST. Schommer et al. (2003) demonstrated that although cortisol habituated upon repeated TSST testing sessions, heart rate did not habituate. These findings suggest that the cortisol response is driven more by the novel, psychosocial component, which wanes upon repeated testing, while the autonomic response is more associated with simple changes in posture, which remain unchanged across repeated testing. Results of the current study further suggest that the control of these stress reactive channels may be controlled differently by the mPFC in men versus women. The primary effects of this are an increased cortisol response in women, and an increased HR response in men. It is unclear how this different pattern may come about. There are well-established sex differences in cortisol reactivity (Kudielka and Kirschbaum, 2005) and in heart rate variability (Snieder et al., 2007) among healthy populations. Damage to the mPFC may have resulted in further alteration of the neural mechanisms controlling these systems, affecting men and women in different ways. Regardless of the exact nature of how this

[1] Correlation analyses of HR and HRV data separated by sex were not possible due to missing data, resulting in small sample sizes.

sex difference may have arisen, a number of studies have documented such sex-related differences in brain function (Cahill et al., 2004; Tranel et al., 2005; Andreano and Cahill, 2009). Given the association between stress reactivity and depression (Monroe and Harkness, 2005) and the increased incidence of depression among women (Kessler, 2003; van Praag et al., 2004), these neuroanatomical differences should be the focus of future work.

Another interpretation of the sex difference in cortisol reactivity following mPFC damage may be that the pattern of damage was different between the men and women in our sample. Some regions of the mPFC are excitatory and some are inhibitory over hypothalamic and brainstem output centers, both within hemispheres (Herman et al., 2005) and between hemispheres (Sullivan and Gratton, 1999). Sullivan and Gratton (1999) showed that lesions to the right infralimbic cortex reduced glucocorticoid responses to stress while left-sided damage did not affect glucocorticoid output. This pattern of differential connections between and within hemispheres could help to explain the current findings. Some of those in the mPFC group may have had damage to areas necessary for stimulatory control over stress reactivity, while others may have had damage to areas necessary for inhibition of stress reactivity. The combination of individuals with such disparate volumes and locations of mPFC damage into one group may have diluted any effect that could be observed in a more homogeneous sample of participants whose damage included only one subregion of the mPFC. The large individual differences in stress reactivity measured using cortisol, heart rate, and subjective reports requires the testing of large groups to detect reliable results. Cortisol responses to the TSST are found in approximately 70% of healthy participants (Kirschbaum et al., 1993). Our results from the current study show a similar pattern of responders to the task across groups (72% in the mPFC group, 67% in the BDC group, and 63% in the NC group; $\chi^2 < 1$).

The reported sex differences lend further support to the idea that the functions of the mPFC are differently distributed in males and females (Tranel et al., 2005). We were unable to test the specific associations among laterality, sex, and stress reactivity in our data due to low sample size in the unilateral mPFC damage groups (e.g., only one female with left-sided damage). It may be the case that there is more redundancy in the connections of the female brain to stress output regions than in males. The volume of damage to the mPFC in females then may not reduce stress reactive output as much as in males. Another possibility is that the combination of subregions of the mPFC that were damaged in the male participants were different from those damaged in the female participants, thereby resulting in the negative association in one sex, but not the other.

Participants with mPFC damage reported greater negative affect, greater feelings of threat, and less control over the stress situation than the other groups. Contrary to the physiological results, this pattern of findings was comparable across both men and women with mPFC damage. The mPFC is purported to play a role in the interpretation of environmental stressors. It may be the case that damage to the mPFC results in an inability to properly assess the threat value of a situation. In the current study, this inability resulted in an exaggerated, as opposed to a reduced subjective experience of threat. Previous work with participants with mPFC damage has shown an impaired emotion regulatory ability, which could manifest as either blunted affect or in emotional outbursts (Anderson et al., 2006; Koenigs and Tranel, 2007). Perhaps this inability to properly recognize the absolute value of the threat posed by the TSST is another example of this alteration in emotion regulation. A number of functional neuroimaging studies have shown activity in mPFC areas during emotional regulation (see Gross, 2007). Emotion regulation may consist of distracting oneself from a negative stimulus or reappraisal of the negative stimulus in a more positive light. A recent study has demonstrated greater mPFC activity during reappraisal than during distraction while viewing negatively affective stimuli (McRae et al., 2009). These findings demonstrate that the conscious effort to reappraise a negative stimulus activates the mPFC. Although it is difficult to directly compare results of functional neuroimaging studies to findings from lesion studies, there is convergence across studies suggesting that the mPFC plays a necessary role in cognitive appraisal such that damage to this region leads to an inappropriate appraisal of negatively emotional situations such as the TSST.

Men in the mPFC group showed greater heart rate and lower high frequency heart rate variability throughout the orthostatic challenge, perhaps due to reduced vagal control over the heart. The mPFC exerts control over the heart and other visceral organs through bidirectional connections via the vagus nerve (Saper, 2002; Thayer and Lane, 2007). Critchley et al. (2003) demonstrated a similar disturbance in cardiovascular control in three participants with damage to the anterior cingulate cortex. These participants exhibited reduced heart rate and systolic blood pressure compared to healthy comparison participants in a mental arithmetic task, and 2 out of 3 showed a pronounced increase in heart rate compared to healthy comparison participants during the standing phase of an orthostatic challenge test. Recent neuroimaging work also supports a role for the mPFC in the chronotropic control of the heart. Lane et al. (2009) demonstrated a positive association between mPFC activity (specifically in the anterior cingulate cortex) and high frequency heart rate variability during emotion induction. Other studies have documented similar correlations between mPFC activity and heart rate variability during performance of mental arithmetic, hand grip (Critchley et al., 2003), and working memory tasks (Gianaros et al., 2004). Reduced control over the heart in this study was demonstrated primarily by a decrease in high frequency heart rate variability during the standing phase of the orthostatic challenge. Interestingly, during the TSST presentation, which is delivered while standing, the mPFC participants' high frequency heart rate variability did not differ from the comparison groups. These findings suggest that although the mPFC exerts tonic control over the heart, during a psychologically stressful task, other neural areas may take up the slack, allowing the individual to produce the appropriate response to the situation. Future work should address the individual effects of postural challenge and psychosocial stress after mPFC damage to better address the role of the mPFC in autonomic control during stress.

The mPFC has been implicated in a wide variety of functions, including emotional regulation and social functions, which may be applicable to understanding its role in the production of the response to psychosocial stress. This study

directly assessed the role of this structure in stress by testing human participants with damage to this region on standard paradigms designed to elicit psychological, autonomic, and endocrine stress reactivity. Findings from the study suggest exaggerated psychological responses to stress that are reflected in physiological reactivity. Several issues remain unanswered from this work, including: which specific subregions of the mPFC are involved in the production of the stress response, do sex and laterality of damage exert differential effects on the stress response, and what are the neural correlates of the autonomic versus endocrine components of the stress response? Future studies from large samples of participants with homogenous lesion location may help to address some of these issues.

Conflict of interest

None declared.

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