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Effects of stress on functional connectivity during problem solving

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ABSTRACT

Aim: Our purpose was to examine how stress affects functional connectivity (FC) in language processing regions of the brain during a verbal problem solving task associated with creativity. We additionally explored how gender and the presence of the stress-susceptible short allele of the serotonin transporter gene polymorphism influenced this effect.

Methods: Forty-five healthy participants (Mean age: 19.6 ± 1.6 years; 28 females) were recruited to be a part of this study and genotyped to determine the presence or absence of at least one copy of the short (S) allele of the serotonin transporter gene, which is associated with greater susceptibility to stress. The participants underwent functional magnetic resonance imaging in two separate sessions (stress and no stress control). One session utilized a modified version of the Montreal Imaging Stress Test (MIST) to induce stress while the other session consisted of a no stress control task. The MIST and control tasks were interleaved with task blocks during which the participants performed the compound remote associates task, a convergent task that engages divergent thinking, which is a critical component of creativity. We examined the relationship between stress effects on performance and effects on connectivity of language processing regions activated during this task.

Results: There was no main effect of stress on functional connectivity for individual ROI pairs. However, in the examination of whether stress effects on performance related to effects on connectivity, changes in middle temporal gyrus connectivity with stress correlated positively with changes in solution latency for individuals with the S allele, but anti-correlated for those with only the L allele. A trend towards a gene × stress interaction on solution latency was also observed.

Discussion: Results from the study suggest that genetic susceptibility to stress, such as the presence of the S allele, affects neural correlates of performance on tasks related to verbal problem solving, as indicated by connectivity of the middle temporal gyrus. Future work will need to determine whether connectivity of the middle temporal gyrus serves as a marker for the effect of stress susceptibility on cognition, extending into stress susceptible patient populations.

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1. Introduction

Decades of research have gone into understanding creativity, such as what mechanisms underlie the process of creative thinking, what makes certain individuals more creative than others, and whether there might be a potential link between creativity and psychopathology. Many different types of tasks have been utilized to assess creativity, including divergent tasks, where participants are asked, for example, to generate novel uses for a tool, and convergent tasks, where participants are asked to derive a specific solution to a problem which requires a high degree of creativity to solve (Beversdorf, 2019). For the purpose of the current paper, we will explore effects on creativity as described for convergent tasks, or the ability to flexibly access remote, scattered resources to come up with an innovative solution to a problem (Heilman et al., 2003). This process requires suppression of what might be the immediate, dominant response and searching for associations that might not be as obvious. Behavioral aspects such as REM sleep (Cai et al., 2009), posture (Lipnicki and Byrne, 2005) and rate of blinking (Chermahini and Hommel, 2010) are known to influence performance on tasks related to creativity in humans wherein the decreased noradrenergic tone associated with more relaxed states proves to be distinctly beneficial for creativity-related tasks (Beversdorf, 2019). Pharmacological manipulations targeting beta-adrenergic receptors in the noradrenergic system have been shown to modulate performance on convergent tasks involving the ability to search through widely distributed networks to come up with solutions on 'unconstrained' cognitive flexibility tasks (Alexander et al., 2007; Beversdorf et al., 1999; Beversdorf et al., 2002). Other manipulations that affect the noradrenergic system would therefore also be expected to affect performance on convergent tasks.

Stress is associated with increased noradrenergic tone, hypervigilance, and narrowed, focused attention. As such, creative thinking is impaired under stressful conditions (Martindale and Greenough, 1973). Numerous studies have reported on the negative behavioral effects of stress on tasks requiring flexible thinking (McEwen and Saplosky, 1995; Sandi, 2013; Shields et al., 2016). For example, manipulation of the noradrenergic system, using the beta-adrenergic antagonist propranolol, has been shown to rescue the negative effects of stress on cognition (Alexander et al., 2007; Faigel, 1991; Laverdure and Boulenger, 1991). Propranolol has shown beneficial effects during creativity tasks that were relatively difficult (Campbell et al., 2008), in relatively easy tasks under conditions of likely upregulated noradrenergic activity such as cocaine withdrawal (Kelley et al., 2007), and in conditions where flexible access to networks may be anatomically restricted, such as autism spectrum disorder (Beversdorf et al., 2008) and Broca's aphasia (Beversdorf et al., 2007). However, since the positive effects of such pharmacological interventions can also be observed in healthy individuals without any history of stress induced cognitive impairment or anxiety (Alexander et al., 2007; Campbell et al., 2008), this suggests that these are fundamental processes of cognition that are not limited to patient populations (Beversdorf, 2019).

Imaging techniques, such as functional magnetic resonance imaging (fMRI) (Beaty et al., 2014; Gold et al., 2012; Green et al., 2012; Jung-Beeman et al., 2004; Zhao et al., 2014), structural MRI (Jung, 2013; Jung et al., 2010; Kühn et al., 2014) and focal cortical stimulation techniques (Green et al., 2017) have helped to better understand the neural basis of creative thinking as well as potential factors that influence an individual's ability to engage in creative thinking (Kenett et al., 2018). Limb and Braun (2008) showed that spontaneous improvisation during a jazz piano performance was accompanied by decreases in activity in frontal regions involved in conscious control. Recent evidence also supports the important role of coordinated functional activation of different brain regions in creativity. High levels of creativity have also been shown to be associated with increased functional connectivity, i.e., temporal correlations between spatially remote neurophysiological events (Friston et al., 1993), between frontal regions engaged in cognitive control and the default mode network that is typically active during wakeful rest (Beaty et al., 2014). However, the neural processes that support creative thinking may be impacted in some situations leading to impaired cognitive performance, such as under situations of stress.

Numerous neuroimaging studies have explored the effects of acute stress on the brain during resting state as well as during cognitive task performance. For example, acute stress is associated with extensive deactivation of the limbic system during rest (Pruessner et al., 2008). Furthermore, activation of brain regions during task performance is also affected by stress. For example, activation of the hippocampus during memory tasks (Qin et al., 2012; Henckens et al., 2009; Pruessner et al., 2007) and prefrontal cortex in a delayed incentive task (Ossewaarde et al., 2011) are affected by acute stressors. Additionally, increased functional connectivity within networks associated with autonomic-neuroendocrine control and vigilant attentional reorienting (Hermans et al., 2011) and increased resting state connectivity between the amygdala and dorsal anterior cingulate cortex, and anterior insula and locus coeruleus (van Marle et al., 2010) have been reported under acute stress. However, the effects of stress on functional connectivity of brain networks that support creative thinking have not been explored.

Some of the variability in creative abilities and stress reactivity across individuals has been attributed to genetic contributions. A polymorphism in the serotonin transporter gene is commonly implicated in heightened stress response (a 43-base pair deletion in the promoter region of the serotonin transporter gene, *SLC6A4*; also known as S-allele, or short allele, in contrast to those without the deletion, referred to as the L-allele, or long allele). Multiple studies have reported that participants with the S-allele experienced greater negative responses to stress exposure (behavioral, neural and maternal genotype effects on offspring) compared to participants without the 43 base pair deletion, or the L-allele (Caspi et al., 2010; Hariri et al., 2002; Hecht et al., 2016; Kenna et al., 2012; van der Meer et al., 2014; Van Der Meer et al., 2015). With the increased response to stress in individuals with at least one copy of the S-allele, there is some preliminary evidence suggesting that performance on verbal problem solving was significantly impaired under stress (Beversdorf et al., 2018). Therefore, we wished to examine how the presence of this genotype might alter functional connectivity in the brain when performing creativity tasks under stress.

Gender is another factor known to influence stress susceptibility. Studies have reported gender-related differences in cortisol secretion levels (Kirschbaum et al., 1992), neural activity (Wang et al., 2007) and cognitive functioning (Lighthall et al., 2012) while under stress. The literature on gender differences in creative tasks is more heterogenous with the overall consensus being that while men and women may not differ in terms of their creative ability, the cognitive strategies, and potentially the neural networks that they apply during creative thinking may be differ (Abraham, 2016; Abraham et al., 2014). Therefore, gender was an additional mediating factor that we considered in this study regarding how stress affects functional connectivity during creative thinking.

In the current investigation, we examined the effects of stress on functional connectivity during the completion of a verbal problem-solving task associated with creativity. We hypothesized that stress would negatively impact performance on the compound remote associates (CRA) task, as previously observed (Alexander et al., 2007). We also hypothesized that functional connectivity under stress between the regions of the brain that have been shown to be activated during administration of the compound remote associates task (such as the left inferior frontal gyrus, left medial frontal gyrus, left middle temporal gyrus, and right superior temporal gyrus (Jung-Beeman, 2005; Jung-Beeman et al., 2004) would be altered by stress and that the effect would be greatest in (1) individuals with at least one copy of the S-allele, compared to individuals homozygous for the L-allele, and (2) females compared to males.

2. Materials and methods

2.1. Participants

A total of forty-five participants (Mean age: 19.5 ± 1.6 years, 28 females) without any significant medical or psychiatric history, including anxiety disorders, were recruited through a weekly e-mail newsletter sent to students enrolled at the University of Missouri. All protocols and procedures were approved by the University of Missouri Health Sciences Institutional Review Board. All participants provided written consent prior to their participation in the study.

2.2. Genetic screening and genotyping

A buccal swab was taken from each participant and was subsequently genotyped for the presence of the short (S-allele) or long (L-allele) polymorphism of the serotonin transporter promoter gene. Genotyping was performed using standard methods (Flexigene kit; Qiagen) as detailed elsewhere (Hecht et al., 2016). Heterozygous carriers of the S-allele were categorized in the S-allele group, and those who were homozygous for the l/l genotype were included in the L-allele group. Furthermore, the presence of the A/G single base substitution on rs25531 (Kenna et al., 2012), T/G single base substitution on rs3813034 (Gyawali et al., 2010), or STin2.10 in Intron 2 VNTR in the l/l genotype (Murphy and Moya, 2011) are known to behave in a less efficient manner and appear more similar to S-allele carriers. Hence, we ran additional genotyping assessments to examine these substitutions. As a result, one participant was regrouped from the L-allele group to the S-allele group based on the presence of the A/G single base substitution on rs25531.

2.3. MRI acquisition and verbal problem solving

Each participant attended fMRI sessions on two different days, separated by at least 24 h. For one half of the participants, the first session was designed to induce stress while the second session was a no stress control session and vice-versa for the other half of the participants. The stress and control conditions were implemented using the Montreal Imaging Stress Test (MIST), a fMRI compatible version of the Trier Social Stress Test (Kirschbaum et al., 1993; Pruessner et al., 1999). The stress condition consists of several timed mental arithmetic tasks with an induced failure component and performance feedback after each run (Dedovic et al., 2005). Based on the practice runs of the subjects, the difficulty of the arithmetic was set to a success rate of 50% to induce the likelihood of failure. Along with a performance indicator that appeared on their screen, the participants were also provided with feedback from the experimenter as a social evaluative threat component. During the no stress control session, the MIST stress block was replaced by simple arithmetic tasks with no time limit or performance feedback.

At the time of the study, participants were unaware that one of the sessions had tasks meant to induce stress. Specifically, participants were informed of a time limit to solve arithmetic problems only before they started the first task in the scanner during the stress session and were given instructions to solve as many of the math problems as they could within the specified time limit. They were also unaware that they would be receiving psychosocial feedback regarding their performance after each run but were instructed that they would be presented with a display of their individual compared to average and expected performance during the task. (Dedovic et al., 2005). After each run, they were reminded that we were tracking their performance and that they needed to do better. During the no stress control session, participants were not given any time limit to solve the math problems while in the scanner nor were they provided with any feedback. Participants were asked to refrain from alcohol, nicotine, and caffeine for 24 h prior to the imaging session. At the start of each session, heart rate and blood pressure were measured in every participant. During the stress session, participants were presented with three iterations of blocks of REST-MIST-TASK, and two runs of this task were acquired (Fig. 1). During the REST block, participants were presented a white screen with cross hair fixation point in the center and no other tasks or stimuli. Each TASK block consisted of six Compound Remote Associates (CRA) problems (Bowden and Jung-Beeman, 2003a, 2003b) presented for 6 s each. The CRA task presented three prompt words and the participant was instructed to think of a word that would form a compound word with all three prompts. (For example: APPLE, CONE, WOOD. Solution: PINE) (Fig. 1). Participants practiced the tasks before the start of the imaging session to ensure that they understood all instructions. The number of correct responses (subjects were asked to indicate with a button press as soon as they thought of a solution to the problem presented) was confirmed with offline testing immediately following the scanning session.

Images were collected using a 3T Siemens Trio Scanner at the University of Missouri Department of Psychological Sciences Brain Imaging Center. Structural T1-weighted images were acquired for anatomical localization (MPRAGE, TR = 1920 m s, TE = 2.9 m s, Angle = 9°, FOV/matrix size = 256 × 256, 176 sagittal slices at 1 mm^3 resolution). Functional T2*-weighted images were acquired to measure the blood oxygenation level dependent (BOLD) response (EPI, TR = 2000 m s, TE = 30 m s, Flip angle = 90°, FOV = 256 × 256, matrix size = 64 × 64, 32 AC-PC aligned slices at 4 mm^3 resolution) during each 6-min run.

2.4. fMRI analysis

FSL (FMRIB Software Library, www.fmrib.ox.ac.uk/fsl) was used to analyze the 4D functional magnetic resonance imaging datasets. FEAT (FMRI Expert Analysis Tool) Version 6.00 was used to perform preprocessing steps including brain extraction using BET (Brain Extraction Tool) (Smith, 2002), slicing timing correction (interleaved) using Fourier-space time-series phase-shifting, motion correction using MCFLIRT (Motion Correction FMRIB's Linear Registration Tool) (Jenkinson et al., 2002), Gaussian spatial smoothing (FWHM (full width half maximum) of 5 mm), high pass temporal filtering (Gaussian-weighted least-squares straight line fitting, cutoff 100 s), grand-mean intensity normalization of the entire 4D dataset and registration of each participant's functional images to the respective high resolution structural image and standardized MNI space (using FLIRT (FMRIB's Linear Image Registration Tool)). Head motion greater than 2 mm along either of the x-, y- or z-axis or any of the rotational axes led to exclusion of the dataset from further analysis. *Z* static images were thresholded using clusters determined by $Z > 2.3$ and a (corrected) cluster significance threshold of $p = 0.05$ (Worsley, 2001).

The Harvard – Oxford Cortical Atlas in FSL was used to create individualized masks for the regions of interest for each subject based on gyral structure. The regions of interest explored were the left inferior frontal, middle frontal, middle temporal, fusiform, and posterior cingulate gyri and inferior parietal lobe and the right superior temporal gyrus due to their known involvement while performing CRA tasks (Jung-Beeman, 2005; Jung-Beeman et al., 2004) (Fig. 2).

The FEATQUERY tool of FSL was used to extract (a) percentage signal change in the BOLD signal within the voxel of maximum activation in each ROI (during task in contrast to rest) and (b) time series of the voxel of maximum activation within each ROI during the task block for each subject (Tivarus et al., 2008). The percentage signal change in BOLD signal was used to examine effects of stress on activation within each ROI that may influence functional connectivity. For functional connectivity analyses, the time series extracted from within task blocks were used to account for the effect of activation magnitude differences between stress conditions on functional connectivity (FC). Bivariate correlations were performed between the time series for each of the ROI pairs. The resulting correlation coefficients were converted using Fisher's *Z* transformation, providing a standardized measure of functional connectivity strength. In order to determine whether overall FC strength changed across all ROIs under the influence of stress, average *z*-scores of correlation coefficients across all ROIs were computed for each individual subject under stress and no stress.

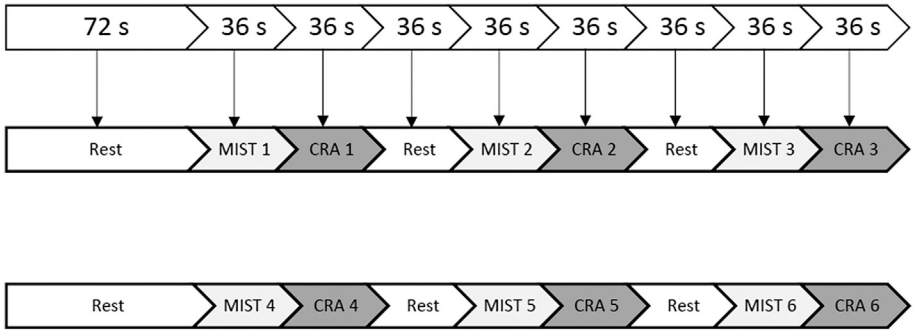

Fig. 1. Stimulus protocol. Stimuli were presented in a block design with repeating units of REST-MIST-TASK. The TASK block consisted of prompts for the Compound Remote Associates (CRA) Task. Each block was 36 s (allowing 6 CRA problems to be presented for the TASK block), except for the REST block at the beginning of the run that was 72 s long.

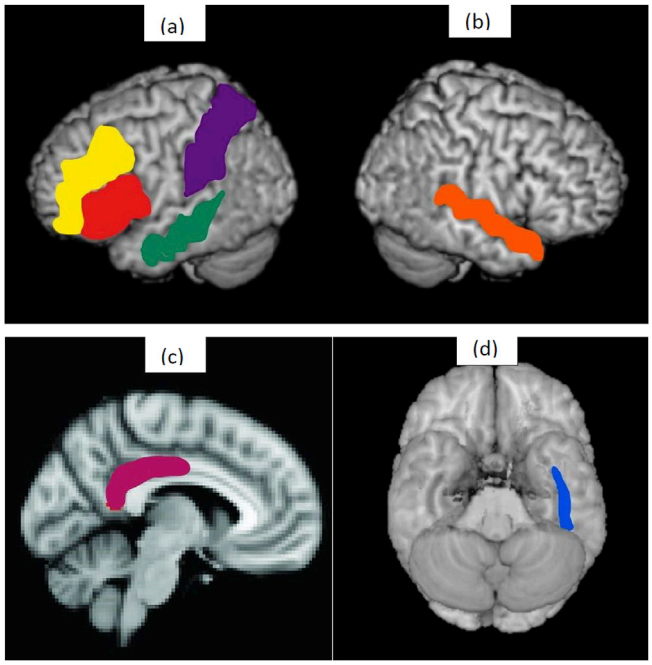

Fig. 2. Regions of interest. The a priori regions of interest (ROIs) explored were (a) left inferior frontal gyrus (red), middle frontal gyrus (yellow), middle temporal gyrus (green), parietal lobe (purple), (b) right superior temporal gyrus (orange), (c) left posterior cingulate gyrus (magenta) and (d) left fusiform gyrus (blue). Masks centered on the a priori regions of interest were created using the Harvard – Oxford cortical atlas in FSL. Percentage signal change and time series from the voxel of maximum activation within each ROI while performing creative tasks under stress and no stress was extracted using the FEATQuery tool of FSL.

2.5. Statistical analysis

Paired sample t-tests were used to determine within-subject differences in (a) number of problems solved under stress and no stress and (b) solution latency under stress and no stress. A series of repeated measures multivariate analysis of variance (MANOVA) tests (SPSS version 24, IBM Corporation) were carried out to examine: (1) activation in the regions of interest: (2 (stress, no stress) x 7 (ROIs)), (2) average functional connectivity across ROIs: (2-way MANOVA, (stress, no stress) x overall functional connectivity) and (3) functional connectivity strength between individual ROI pairs: (2 (stress, no stress) x 21 (ROI pairs)). Gender and genotype were included as between subject factors. Bivariate correlations were performed between differences in task performance measures and change in functional connectivity strengths between the regions under stress and no stress to understand the the relationship between functional connectivity strength and task performance. Bonferroni corrections for multiple comparisons were applied to all analyses and the results reported here survived correction.

3. Results

3.1. Demographics

fMRI data from 32 participants was analyzed (5 participants were dropped from the study because they did not attend the second session and data from 8 participants was not included in further analysis due to excessive motion, as defined by exceeding 2 mm along either the linear or rotational axes as mentioned above). 18 participants underwent the no stress session first while 14 of them underwent the stress session first. All the analyses were repeated including task order as between subjects' factor to account for possible task order effects. Of the 32 participants included in the final analysis, there were 11 male participants, and 15 participants had at least one copy of the S-allele (Table 1). Only 5 participants had the s/s allele type which was too small a sample for separate analysis, so they were included with the heterozygous group, as with previous work (Hecht et al., 2016; Beversdorf et al., 2018).

3.1.1. Stress induction

Heart rate and blood pressure were recorded immediately prior to imaging, 60 min into the imaging session and after the imaging session (at 120 min). No significant differences in heart rate were observed for either stress condition at any of the time points measured. However, paired sampled t-tests revealed that both systolic and diastolic blood pressures were significantly higher midway during the imaging (Systolic: 117.4 ± 11.0 std dev, $t(33) = -2.563$, $p = 0.015$; Diastolic: 73.8 ± 12.9 std dev, $t(33) = -2.055$, $p = 0.048$) and post imaging (Systolic: 115.9 ± 11.3 std dev, $t(33) = -2.095$, $p = 0.044$; Diastolic: 74.9 ± 10.9 std dev, $t(33) = -2.672$, $p = 0.012$) compared to pre-imaging on the stress day (Systolic: 111.4 ± 13.7 std dev, Diastolic: 68.7 ± 10.4 std dev). While one of these measures, diastolic blood pressure was also found to be elevated midway during imaging (70.9 ± 9.1 std dev, $t(33) = -2.167$, $p = 0.038$) and post imaging (71.5 ± 8.3 std dev, $t(33) = -3.539$, $p = 0.001$) compared to pre-imaging on the no stress control day (67.1 ± 8.0 std dev), the elevation in diastolic pressure post imaging (74.9 ± 10.9 std dev) was still found to be higher on the stress induction day compared to the no stress control day (71.5 ± 8.3 std dev, $t(33) = 1.997$, $p = 0.05$), suggesting that although there is some inherent stress that may be related to the imaging procedures, the induction of stress was greater during the stress compared to control conditions. Blood pressure changes have previously been shown to be impacted by the TSST (Alexander et al., 2007), thus supporting that a stress response was induced by the MIST in this study.

Table 1
Demographics of participants.

	Total (n = 32)	Male	Female	X^2	P	S-allele (n = 15; s/s = 5; s/l = 10)	L-allele (n = 17)	X^2	P
AGE (YEARS)	**19.9 (1.6)**	19.7 (2.0)	20.1 (1.5)	10.72	0.097	19.9 (1.2)	20.1 (2.0)	8.44	0.208
GENDER (M/F)	**11/21**	_	_	_	_	5/10	6/11	_	_

Group comparisons were performed using Chi-square test. All values are shown as mean (SD). M = male, F = female.
Of the 15 S-allele participants, 5 participants had the s/s allele type and 10 had the s/l allele type.

3.2. Verbal problem solving

A paired samples *t*-test revealed that there was no significant change in the number of problems correctly solved under stress (Mean(*SD*) = 9.0(3.7)) and no stress (Mean(*SD*) = 8.9(3.8)) ($t = 0.05$, $p = 0.9$). We then examined solution latency for problems that were correctly solved to determine whether the impact of stress affected problem solving speed. A stress × genotype interaction exhibited a trend ($F(1,23) = 7.260$, $p = 0.06$) but no significant differences between stress and control were observed in either genotype group in post hoc *t*-tests (Fig. 3).

3.3. ROI activation and functional connectivity

Group activation maps for the CRA task are shown in Fig. 4. Table 2 gives information on sizes of regions of interest and positions of voxels of maximum activation within regions of interest in standard space (in mm).

As an initial exploration we assessed whether there were overall effects of stress on activation or connectivity. A repeated measures MANOVA did not reveal a significant effect of stress ($F(1,28) = 0.01$, $p = 0.91$), or stress x gender ($F(1,28) = 1.49$, $p = 0.23$) or stress x genotype ($F(1,28) = 0.11$, $p = 0.74$) interaction on activation across the ROIs. On Bonferroni corrected assessment of individual ROIs, to examine for focal effects, a significant stress × gender interaction effect was observed on percentage signal change within the voxel of maximum activation in the right superior temporal gyrus ($F(1,28) = 4.49$, $p = 0.04$) (Fig. 5). Post hoc *t*-tests revealed that males showed a significantly greater percentage signal change in the voxel of maximum activation within this region while performing the CRA task under stress compared to females (t(32) = 2.22, p = 0.03). We did not observe any other significant changes in percentage signal change under stress and no stress in any of the other ROIs examined.

There were no significant effects of stress ($F(1,28) = 0.43$, $p = 0.51$) or stress x gender ($F(1,28) = 0.41$, $p = 0.53$) and stress x genotype ($F(1,28) = 0.007$, $p = 0.93$), or three-way interactions on overall functional connectivity across all ROIs. The possible effects on individual

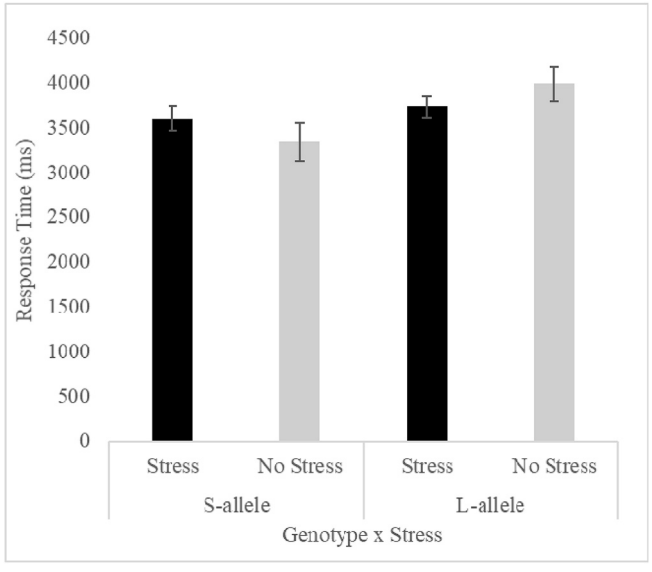

Fig. 3. Verbal problem solving. A stress × genotype interaction effect trending towards significance was observed ($F(1,23) = 7.26$, $p = 0.06$) for solution latency on only problems where correct responses were recorded. While the S-allele group had numerically slower response time under stress, post hoc t-tests did not reveal significant differences between individual groups.

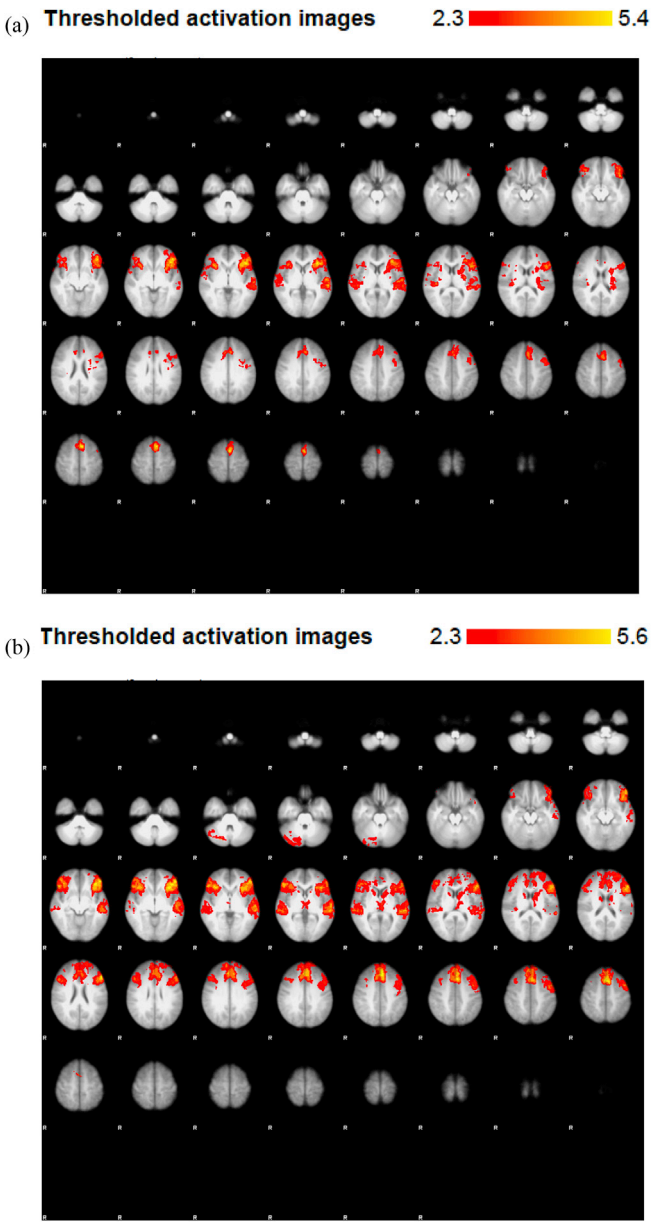

Fig. 4. Group activation maps. Group activation maps for participants (n = 32) performing the Compound Remote Associates task under (a) stress and (b) no stress. Significant stress × gender interaction effect was observed on percentage signal change only in the right superior temporal gyrus. Males showed a significant increase in percentage signal change in this region while performing the CRA task under stress compared to females.

Table 2
Sizes of regions of interest and positions of voxel of maximum activation.

	Number of Voxels	Position of voxel of maximum activation in standard space (mm)		
		x	y	z
Left Inferior Frontal Gyrus	101	−48	23.2	−10.6
Left Middle Frontal Gyrus	192	−43.8	16.8	24.5
Left Middle Temporal Gyrus	168	−59.7	−40.2	−23.6
Left Parietal Lobe	49	−60.8	−36	32
Right Superior Temporal Gyrus	425	69.6	−16.5	6.2
Left Posterior Cingulate Gyrus	129	−1.2	−47.6	10.2
Left Fusiform Gyrus	68	−11	−93	−22.6

ROIs pairs was of interest, and therefore, repeated measures MANOVAs were conducted for each individual pair, with Bonferroni corrections for multiple comparisons across individual pairs. Examining each ROI pair, a three-way interaction effect for stress x gender x genotype was observed on the functional connectivity strength between the left inferior frontal gyrus and the left middle temporal gyrus ($F(1,28) = 5.26, p = 0.03$). Post hoc *t*-tests revealed that males who were heterozygous or homozygous for the S-allele displayed significantly lower strength of functional connectivity between the regions when attempting verbal problem solving under stress compared to both females with at least one copy of the S-allele ($t = -2.418, p = 0.03$) and homozygous L-allele males ($t = -3.44, p = 0.007$). Males who were homozygous for the L-allele were also found to have significantly greater strength of functional connectivity between the left inferior frontal and middle frontal gyrus compared to homozygous L-allele females when under stress ($t = 2.209, p = 0.04$) (Fig. 6). No significant differences were observed between the individual groups for the stress vs. no stress comparison.

3.4. Activation, functional connectivity and task performance

To examine how the effect of stress on performance related to the effect of stress on functional connectivity, we examined whether changes in solution latency during stress, as compared to control, were related to changes in functional connectivity. Bivariate correlations were computed between the difference in solution latency while under stress compared to control and (a) difference in average functional connectivity across all ROIs under stress and control and (b) differences in functional connectivity between individual ROI pairs under stress and no stress. For heterozygous or homozygous S-allele participants, regardless of gender, we observed that differences in solution latency due to stress were positively correlated with the change in functional connectivity strength between the left middle temporal gyrus and the left posterior cingulate gyrus ($r = 0.65, p = 0.03$). For homozygous L-allele participants, changes in solution latency were negatively correlated with differences in functional connectivity strength between the left inferior frontal gyrus and left middle temporal gyrus ($r = -0.57, p = 0.04$).

As mentioned previously, all the analyses were repeated including task order as between subjects' factor to account for possible task order effects. However, when task order was included in the analysis, there was no change in results.

4. Discussion

The objective of this investigation was to examine the neural correlates of the impact of stress on a verbal problem-solving task, the CRA, a convergent task often used to study creativity (Bowden and Jung-Beeman, 2003a,b), utilizing the Montreal Imaging Stress Test (Pruessner et al., 1999) to induce stress in subjects in the imaging environment. Stress is known to impair performance on tasks requiring flexible access to remote, distributed networks due to heightened arousal and narrowed focus (Martindale and Greenough, 1973). As a result, stress has a direct effect on the neural substrates associated with performing tasks that require the generation of creative solutions such that the use of creative solution pathways is overridden by possibly more dominant, less creative pathways. We did not observe differences in number of CRA tasks solved by the participants under stress and control conditions. However, solution latency, a more sensitive measure, showed a trend towards significance in a genotype specific manner. The observed result is in the same direction as had been noted in a previous study where participants with at least one S-allele performed worse on an anagrams task under stress compared to the no stress control condition (Beversdorf et al., 2018). It should be noted that the set of problems used in the imaging environment in the present study was smaller than the set of problems used in the previous behavioral study (Beversdorf et al., 2018), impacting the robustness of the behavioral results in the imaging environment. However, the imaging findings are of interest.

Regarding functional activation differences, there was no main effect of stress, and the only isolated finding observed across ROIs was

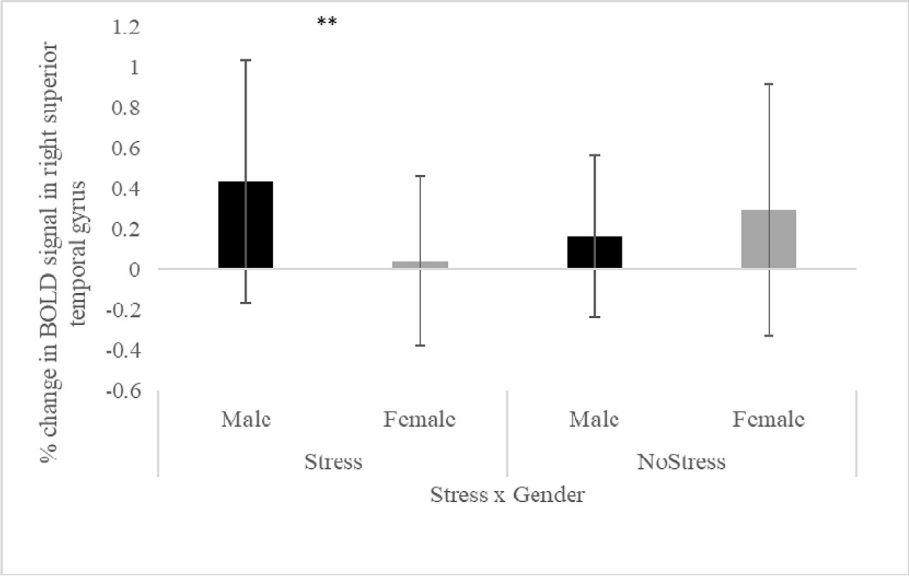

Fig. 5. ROI activation. A significant stress × gender interaction effect was observed on activation in the right superior temporal gyrus ($F(1,28) = 4.49, p = 0.04$). Post hoc *t*-tests showed that males had greater activation in the region while attempting CRA tasks as compared to females during stress ($t = 2.22, p = 0.033$).

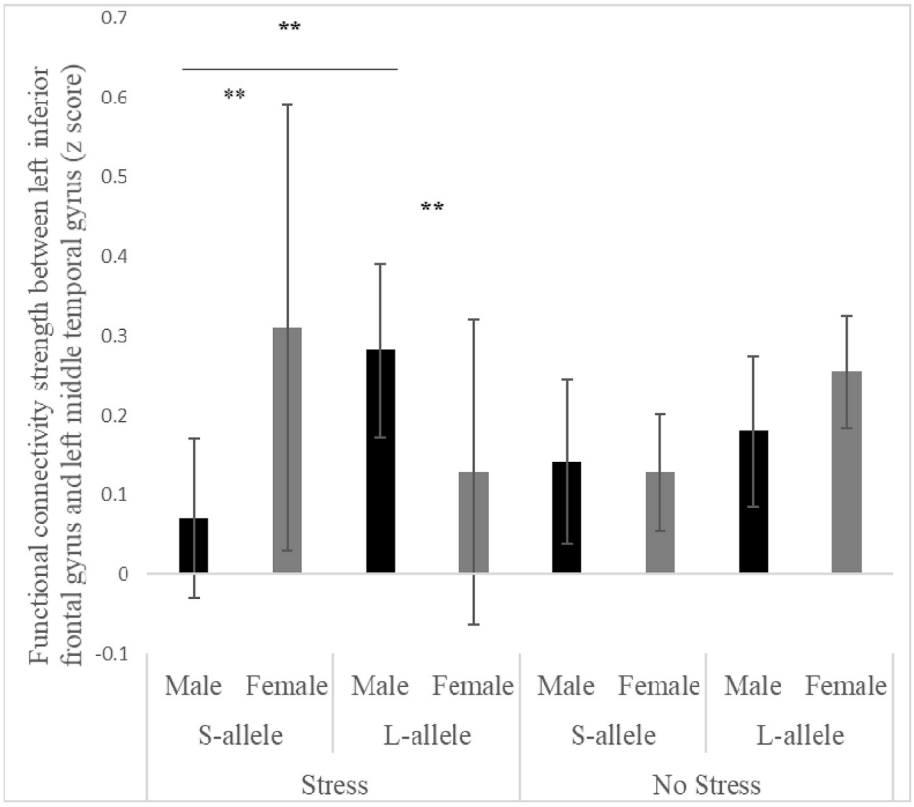

Fig. 6. Functional connectivity results. A three-way interaction effect for stress x gender x allele was observed on functional connectivity between the left inferior frontal gyrus and the left middle temporal gyrus. Post hoc t-tests revealed that S-allele males had reduced strength of functional connectivity compared to S-allele females and L-allele males during creativity task under stress. L-allele males were found to have significantly greater strength of functional connectivity between the regions than L-allele females when verbal problem solving under stress (** = $p < 0.05$).

increased mean activation in the right superior temporal gyrus in males compared to females during verbal problem solving under stress. Activation in the right superior temporal gyrus during verbal creative tasks, consistent with what has been observed here, have been reported previously (Boccia et al., 2015). Previous studies have also described a role for the right superior temporal gyrus in maintaining solution related activation to problems that are yet to be solved (Bowden and Jung-Beeman, 2003a; Zhao et al., 2014). Therefore, it is possible that male participants in this study may have deliberated more on the problems they were unable to solve, leading to greater activation in the region, compared to female participants, but this finding needs to be interpreted with caution until replicated in larger samples.

The results from our functional connectivity analyses revealed that the presence of the S- and L-alleles of SLC6A4 (SERT gene) differentially impact the coordinated functional activation in response to stress during cognitive flexibility tasks in males and females. While performing a task requiring cognitive flexibility under stress, males who were either heterozygous or homozygous for the S-allele displayed decreased strength of functional connectivity between the left inferior frontal gyrus and the left middle temporal gyrus when compared to both female hetero- and homozygous carriers of the S-allele and males who were homozygous for the L-allele. Males who were homozygous for the L-allele however, displayed greater strength of functional connectivity between the regions under stress compared to homozygous L-allele females. Thus, gender appears to impact the effect of the SERT gene on coordinated functional activation during stress, such that stress reactivity in individuals with reduced efficiency of serotonin reuptake may have a different impact on functional network integration in males compared to females. While creative thinking does require access to remote, non-dominant pathways in the brain, there appears to be individual variability in the connectivity between brain regions associated with creativity. One study found that resting state connectivity of the left inferior frontal gyrus with the default mode network was greater among participants yielding the best performance on divergent thinking tests (Beaty et al., 2014). In S-allele carrier males, stress appears to lead to a greater reduction of this left inferior frontal gyrus connectivity to the left middle temporal gyrus, compared to S-allele carrier females or homozygous L-allele males. However, any conclusions drawn from stress x gene × gender interactions should be taken with extreme caution, due to the small sample size of the subgroups.

Finally, and most critically, *SLC6A4* genotype was also found to influence the association between changes in solution latency and changes in functional connectivity strength between specific brain regions under stress compared to control. Specifically, left middle temporal gyrus functional connectivity positively correlated with performance changes during stress in hetero- and homozygous S allele participants, but negatively correlated with performance changes during stress in homozygous L allele participants. Gender did not appear to have an effect on this relationship. Thus, the effect of stress on connectivity of the left middle temporal gyrus relates to effects on performance, but the relationship differs across individuals with differing genetic susceptibility to stress. This provides further support for individual differences in cognitive responses to stress, where genetics is one potential contributory factor.

These results show that stress may affect functional activation and network connectivity in the brain during creative problem solving in a genotype specific manner, as indicated by *SLC6A4* genotype, with possible gender-specific effects. With this difference in the effect of stress on left middle temporal gyrus connectivity during problem solving, it will be of interest to see whether this connectivity response serves as a marker for other populations with cognitive susceptibility to stress, such as individuals with test anxiety, performance anxiety, or other anxiety-related disorders. Additionally, highly creative people have been documented to have increased incidence of depression, bipolar disorder and/or schizophrenia (Andreasen, 2008; Power et al., 2015), and people with greater schizotypy are known to perform well on insight tasks of creativity (Karimi et al., 2007). Therefore, exploring functional activation and network connectivity in the aforementioned populations would be of interest. It will also be of interest to determine how the cognitive effects

of stress directly relate to activity of the catecholaminergic systems. The dopaminergic system, and its associated genes (Reuter et al., 2006), and noradrenergic system, as demonstrated by its modulation using pharmacological intervention (Alexander et al., 2007), provide further evidence of the importance of looking in this direction. Additionally, different types of creativity other than convergent tasks (Beversdorf, 2019) need to be assessed in future analysis. The results from these analyses will help get a more complete understanding of how stress modulates functional connectivity in the brain associated with cognitive flexibility in healthy as well as clinical populations.

5. Limitations

There are some limitations that must be taken into consideration while interpreting the results of this study. For one, the three-way interaction results must be interpreted with caution due to the small sample size in each subgroup. Future studies will need to look at other potential regions as well, to see if there are important effects on other networks more broadly distributed than the targeted task-related regions examined herein. Also, only a trend was detected for the interaction effect between stress and genotype for solution latency, possibly due to the smaller number of tasks administered in the imaging environment, but the trend was in the same direction as our previous findings (Beversdorf et al., 2018). Additionally, reliable cortisol levels were not available in this study to reaffirm the induction of stress due to problems with the samples. However, we were able to detect significant changes in blood pressure as an indication of reliable induction of stress.

6. Summary

We examined the influence of stress, gender and *SLC6A4* genotype on functional activation and connectivity during creative thinking. Genetic susceptibility to stress affected the relationship between stress and performance with left middle temporal gyrus-inferior frontal gyrus functional connectivity. Thus, the neural response to stress for processes that are involved in creative thinking can vary with the influence of genetics. Future studies will need to confirm these preliminary findings and determine whether the connectivity effects observed in the more genetically stress susceptible individuals observed in this study are also observed in patient populations with enhanced cognitive susceptibility to stress, such as test anxiety and performance anxiety. The discovery of such differences might serve towards the development of biomarkers for enhanced cognitive susceptibility to stress.

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Informed consent statement

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) with the Helsinki Declaration of 1975, and the applicable revisions at the time of the investigation. Informed consent was obtained from all patients for being included in the study.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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