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Influence of Serotonin Transporter *SLC6A4* Genotype on the Effect of Psychosocial Stress on Cognitive Performance: An Exploratory Pilot Study

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Abstract

Background and Objective—Previous research has shown an effect of various psychosocial stressors on unconstrained cognitive flexibility, such as searching through a large set of potential solutions in the lexical-semantic network during verbal problem-solving. Functional magnetic resonance imaging has shown that the presence of the short (S) allele (lacking a 43–base pair repeat) of the promoter region of the gene (*SLC6A4*) encoding the serotonin transporter (5-HTT) protein is associated with a greater amygdalar response to emotional stimuli and a greater response to stressors. Therefore, we hypothesized that the presence of the S-allele is associated with greater

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stress-associated impairment in performance on an unconstrained cognitive flexibility task, anagrams.

Methods—In this exploratory pilot study, 28 healthy young adults were genotyped for long (L)-allele versus S-allele promoter region polymorphism of the 5-HTT gene, *SLC6A4*. Participants solved anagrams during the Trier Social Stress Test, which included public speaking and mental arithmetic stressors. We compared the participants' cognitive response to stress across genotypes.

Results—A Gene $\times$ Stress interaction effect was observed in this small sample. Comparisons revealed that participants with at least one S-allele performed worse during the Stress condition.

Conclusions—Genetic susceptibility to stress conferred by *SLC6A4* appeared to modulate unconstrained cognitive flexibility during psychosocial stress in this exploratory sample. If confirmed, this finding may have implications for conditions associated with increased stress response, including performance anxiety and cocaine withdrawal. Future work is needed both to confirm our findings with a larger sample and to explore the mechanisms of this proposed effect.

Keywords

stress; problem-solving; semantic; creativity; *SLC6A4*

For some time, it has been proposed that flexible thinking is susceptible to the effects of stress (Martindale and Greenough, 1973). In our own previous work (Renner and Beversdorf, 2010), we induced impairments in convergent thinking tasks that require a high degree of flexibility of access to lexical/semantic/associative networks by using experimental psychological stressors. An example would be watching a very stressful movie scene such as the beginning of *Saving Private Ryan* (Renner and Beversdorf, 2010). In another study (Alexander et al, 2007) using the Trier Social Stress Test (TSST) (Kirschbaum et al, 1993), we found that psychosocial stressors impaired unconstrained cognitive flexibility, and the noradrenergic antagonist propranolol reversed the cognitively impairing effects of stress. Recognizing inherent differences in stress reactivity, we undertook the present study to explore the genetic factors that may affect how individuals vary with respect to the effects of stress on their cognition.

We are particularly interested in how variations in the serotonin transporter (5-HTT) might affect different aspects of stress reactivity, as discussed in our examination of the effects of prenatal stress on development (Hecht et al, 2016). Variations in the 5-HTT protein are known to affect stress reactivity. Specifically, a 43-base pair insertion/deletion polymorphism in the promoter region (5-HTTLPR) of the serotonin transporter gene, *SLC6A4*, producing a short (S) or long (L) allele, has been shown to have an effect on stress tolerance. The 43-base pair deletion (S-allele) in the 5-HTTLPR region is associated with a decrease in *SLC6A4* transcription and expression (Bengel et al, 1998; Heils et al, 1996; Lesch et al, 1996; Perez and Andrews, 2005; Prasad et al, 2005). Thus, carriers of the S-allele have significantly less serotonin clearance, resulting in increased levels of the neurotransmitter in the extracellular space (Perez and Andrews, 2005).

While there are some equivocal findings on the binding potential and effects on messenger RNA expression across *SLC6A4* genotypes directly at the 5-HTT (Lim et al, 2006), long-

term and perhaps more subtle differences in serotonergic signaling associated with the *SLC6A4* genotype are evident in positron emission tomography studies examining specific serotonin receptors, including 5-HT1A (Baldinger et al, 2015; David et al, 2005; Lothe et al, 2009) and 5-HT4 (Fisher et al, 2012). This indirect effect on 5-HT1A expression is observed even in nonhuman primates that carry the *SLC6A4* promoter polymorphism (Christian et al, 2013).

It has been shown that this alteration in the serotonergic system in S-allele carriers results in emotional and behavioral abnormalities, particularly an increase in stress reactivity. For example, the S-allele is associated with personality traits such as neuroticism and anxiety-related disorders (Domschke and Dannlowski, 2010; Sen et al, 2004). One large study suggested that the S-allele is associated with the development of depression after major life stressors (Caspi et al, 2003). While some subsequent studies suggested that this link was not present (Risch et al, 2009), a later meta-analysis was again supportive of the link (Karg et al, 2011). Therefore, findings on the association of the S-allele with psychiatric conditions are quite mixed.

Other studies have found that the presence of the S-allele can provide some advantages in certain settings, including social cognition (Homborg and Lesch, 2011). Furthermore, L-allele carriers have been shown to have increased cortisol response to stress among the youngest and oldest populations (Mueller et al, 2011), and whether the S-allele or the L-allele is associated with depression in association with stress can depend on a person's gender (Brummett et al, 2008). Also, the L-allele has been reported to be associated with greater serotonin metabolites in the cerebrospinal fluid and with cardiovascular responses during a mental stress protocol (Williams et al, 2001).

Regarding the effects of acute stress, imaging evidence suggests that individuals who have at least one copy of the S-allele have increased reactivity to this type of stress (Hariri and Weinberger, 2003; Munafò et al, 2008). Furthermore, individuals with the S-allele have increased activation of the amygdala (critical for emotional reactivity) and decreased activity in the prefrontal cortex (critical in planning) in response to acute stress, with decreased connectivity between these prefrontal and amygdalar regions (Ossewaarde et al, 2011; van Wingen et al, 2012; Volman et al, 2013), suggesting a reduced ability of the prefrontal cortex to inhibit amygdalar activation. Stress also increases the connectivity of the amygdala with other brain regions, including the fronto-insular area, dorsal anterior cingulate cortex (Hermans et al, 2011; van Marle et al, 2010), inferotemporal region, temporoparietal region, thalamus, hypothalamus, midbrain (Hermans et al, 2011), and pons (including the area of the locus ceruleus) (van Marle et al, 2010). Individuals with S-alleles have also been shown in a meta-analysis to have greater hypothalamic-pituitary-adrenal axis activation in response to acute psychological stress (Miller et al, 2013), particularly for SS homozygotes, and greater cardiovascular reactivity has also been observed, affecting heart rate (HR) and blood pressure (Way and Taylor, 2011).

Therefore, we performed a pilot study to examine in an exploratory manner what, if any, impact the presence of the S-allele had on cognitive performance. To answer this question,

we evaluated the performance of our participants on an unconstrained cognitive flexibility task (anagrams) in the setting of the TSST.

METHODS

Participants

Participants were 28 healthy adults (14 men, 14 women) with a mean age of 26 years (standard deviation = 7.20). These participants were recruited through flyers posted on the Ohio State University campus and Internet-based postings as part of participation in one of several ongoing studies on stress and cognition, including Alexander et al (2007). Exclusion criteria were known histories of learning disabilities, such as dyslexia, phobia regarding math or giving speeches, or any other history of an anxiety disorder. In addition, non-native English speakers were excluded, as well as smokers and people who were unable to abstain from caffeine, alcohol, and intense exercise for 12 hours before each session. Procedures were performed in accordance with the Biomedical Sciences Institutional Review Board of the Ohio State University. We obtained written informed consent from all participants before initiating any aspect of the work.

Experimental Design

Participants reported to the General Clinical Research Center of the Ohio State University for two visits with 5 to 7 days between the visits. Participants were pseudorandomly assigned to either the Stress or Control (no stress) condition at their first visit, and to the opposite condition on the second visit. Ordering of Stress and Control conditions was counterbalanced between participants. Upon his or her arrival for each visit, after a 15-minute adaptation period, instructions for the modified TSST stress or control tasks were relayed to the participant (Kirschbaum et al, 1993).

Stress and Control Conditions—We used the stressor paradigm described in our previous work (Alexander et al, 2007). A modified TSST (Kirschbaum et al, 1993) was used to elicit stress and to determine its effects on cognitive performance.

For the Stress condition, participants were asked to deliver a 5-minute speech supporting their candidacy for employment in a law office or for admission into graduate business school. The speech task (TSST verbal component) was followed by a 5-minute mental arithmetic task, as described in our previous work (Alexander et al, 2007). These tasks were performed in the presence of panelists who were wearing white laboratory coats, were taking notes, and had been instructed not to provide any signs of positive reinforcement. Additionally, video cameras and audio recorders were present during the Stress condition, and the participants were informed that their performance would be subsequently judged by behavioral analysts.

For the Control condition, no panelists or recording devices were present, and participants were asked to read aloud a designated passage and to count alone in a room, doing each for 5 minutes.

Cognitive Tasks—We used the cognitive flexibility tasks described in our previous work (Alexander et al, 2007). Participants were interrupted 1 minute after the beginning of the speech or passage-reading task and asked to perform the cognitive task (anagrams). After finishing the cognitive task, participants resumed the TSST verbal component (speech delivery or reading aloud).

At 1- or 2-minute timed intervals, the TSST component (5-minute speech or 5-minute mental arithmetic) was again interrupted and the next cognitive task was administered. Participants were instructed to focus on the cognitive task at hand, rather than on keeping track of their place within the verbal or mathematical task. Participants were told that the experimenters would remind them of where they had stopped in their speech or arithmetic task. Blood pressure and HR were taken before initiation of the Stress condition task, as well as during a break in the middle of it.

Anagram Task: In order to assess effects on unconstrained cognitive flexibility for access to lexical-semantic networks, one of multiple versions of an anagram task was administered at each experimental session. The order of test versions was presented in a counterbalanced manner across conditions. The anagram task required unscrambling three 5-letter words, six 6-letter words, and six 7-letter words, each word within 30 seconds. Three separate presentations (one presentation per interruption) of five anagram problems (one 5-letter word and two each of the 6- and 7-letter words per presentation) were administered within each session. As with our previous work (Alexander et al, 2007; Beversdorf et al, 1999, 2002; Campbell et al, 2008), the natural logarithm of latency to solve the anagram was recorded and summed for each session to derive latency scores. Unsolved anagrams were recorded as 30 seconds. Anagram problem-solving has been used previously as a method of assessing creativity (Gavurin, 1975; Kumar and Kumari, 1988; Shaw and Conway, 1990).

Visual-Motor Control: The Grooved Pegboard Test (Lafayette Instruments, Lafayette, Indiana) was administered at each experimental session. The purpose of this task was to assess processing speed as well as visual-motor coordination and manual dexterity. Participants were instructed to insert grooved pegs into randomly positioned slots on the board as quickly as possible. Performance, which is determined by speed of completion of the task, served as a control for processing speed, since latency for problem-solving was the measure used for the anagram task.

Genotyping—We used the same genotyping methods described in our previous work (Hecht et al, 2016). Blood was drawn via a standard venipuncture from the median cubital vein of the arm. Genomic DNA was obtained from the subjects' whole blood (Flexigene kit; Qiagen, Germantown, Maryland) according to the manufacturer's instructions. Polymerase chain reaction was performed as previously described (Wendland et al, 2006). Briefly, the 5-HTTLPR was amplified using the Qiagen polymerase chain reaction kit from 25 ng of genomic DNA using the following primers: 5'-TCCTCCGCTTTGGCGCCTCTTCC-3' (Forward) and 5'-TGGGGGTTGCAGGGGAGATCCTG-3'. Cycling conditions were as follows: 95°C for 15 minutes followed by 35 cycles of 94°C for 30 seconds, 65.5°C for 90 seconds, and 72°C for 60 seconds, with a final extension step of 72°C for 10 minutes. Polymerase chain reaction products were then loaded onto a 3.5% agarose gel and run for 1

hour at 160V. Bands were visualized with SYBR safe DNA gel stain (Invitrogen, Carlsbad, California) with 469 base pairs and 512 base pairs identifying the S- and L-alleles, respectively, to identify the presence of the L- versus S-allele of the 43-base pair repeat in the 5-HTT gene.

Statistical Analysis

Cognitive data were analyzed using a 2-factor analysis of variance for all measures between genetic variance (S-allele versus L-allele, between subjects), and between the two experimental sessions (Control versus Stress, within subject). Post hoc comparisons were analyzed using one-way analysis of variance or paired-sample *t* tests, including the predicted comparison within the S-allele group to see if the cognitive effect of the TSST is observed within this group.

We set statistical significance at 0.05.

RESULTS

Genotyping

The genotype frequencies for our 28 participants were LL = 7, LS = 13, and SS = 8 (L-allele frequency = 0.48, S-allele frequency = 0.52), which is in Hardy-Weinberg equilibrium. Thus, 21 of our participants were carriers of the S-allele.

Cognitive Performance

Anagrams—Analysis of variance revealed no main effect of gene or stress on anagram performance, but a significant Gene $\times$ Stress interaction effect ($F_{1,26} = 4.64$, $P = 0.041$) was detected, as limited by the small number of LL participants. However, subsequent *t* tests revealed that for the subjects with at least one S-allele, performance was significantly worse during the Stress than the Control (no stress) condition ($t_{20} = 2.299$, $P = 0.032$), whereas there was no such difference in the participants in the limited sample with no S-allele (Table 1, Figure 1).

Visual-Motor Control—There was no statistically significant effect of stress on visual-motor speed in the Grooved Pegboard Test within either the S-allele or the no S-allele group on individual *t* tests (Table 1).

Heart Rate and Blood Pressure

During the Stress condition, HR did not change from the beginning of the session to the middle of the stress task (mean $\pm$ standard deviation baseline HR, 76.7 ± 10.7 ; stress HR, 78.1 ± 16.8 ; $P =$ not significant), but systolic blood pressure (SBP) did significantly increase (baseline SBP, 119.9 ± 21.8 ; stress SBP, 136.8 ± 26.0 ; $P = 0.003$). The same pattern was observed when only the S-allele participants were assessed (baseline HR, 76.8 ± 11.6 ; stress HR, 76.4 ± 18.0 ; $P =$ not significant; baseline SBP, 121.1 ± 25.5 ; stress SBP, 132.6 ± 24.6 ; $P = 0.01$).

DISCUSSION

Our results from this exploratory sample suggest that the presence of the 5-HTT genotype with at least one S-allele may affect cognitive flexibility in response to stress, particularly for problem-solving tasks that require a high degree of flexible access to lexical-semantic networks. However, this exploratory assessment, taken from existing samples from individuals who participated in studies on stress and cognition, needs to be confirmed in a larger sample. Interestingly, in this study we did not detect a main effect of stress, in contrast to the findings of our previous work (Alexander et al, 2007). However, between-subject variability in cognitive response to the TSST appeared to be an important factor, as there was a significant impairing effect of stress in those who had at least one copy of the S-allele, the allele associated with a greater response to acute stress in imaging studies (Hariri and Weinberger, 2003; Munafò et al, 2008).

The sample was too small, however, to draw any conclusions about the statistical lack of effect among those with no S-allele, which also limits the conclusions that can be drawn from the interaction effect observed. While it might appear that L-allele participants performed better than S-allele participants (Figure 1), the small sample of L-allele participants limits any interpretation of this, and with between-subject comparisons, none of the differences between genetic groups for either of the compared conditions (Stress or Control) reached significance. Still, the effect of stress on S-allele participants is of at least preliminary interest, as it benefits from the statistical power of within-subject comparison and a larger sample than the no S-allele group.

As solution latency was the measure used to monitor performance, we also assessed whether there was a general effect on motor speed that might be driving performance effects, but we detected no effect on motor processing speed. Because effects of the stressor on SBP appeared to be present in all participants, our findings would not likely be confounded by issues such as differential allele effects on sympathetic activity as assessed by cardiovascular reactivity (Williams et al, 2001).

The serotonergic system plays several important roles in cognition. It is involved with balancing the weights of reward and punishment, along with dopamine (Krantz et al, 2010). Tryptophan depletion enhances punishment prediction but does not affect reward prediction (Cools et al, 2008), and serotonergic neurons appear to signal reward value (Nakamura et al, 2008). Furthermore, prefrontal serotonin depletion affects reversal learning, but not set-shifting (Clarke et al, 2005). These aspects of cognition will be important to monitor in future studies exploring the effects of serotonin-associated polymorphisms on the type of problem-solving in our study.

Our focus, though, was on the importance of the 5-HTT polymorphism in the reactivity of the stress response system. Previous research has shown increased activity of the amygdala that is associated with acute stress in individuals with the S-allele, as well as altered connectivity of the amygdala to other cortical, subcortical, and brainstem regions (Hermans et al, 2011; Ossewaarde et al, 2011; van Marle et al, 2010; van Wingen et al, 2012; Volman

et al, 2013). The imaging correlates of the interaction between genotype, stress, and problem-solving have not yet been explored.

Some effects of 5-HTT genotype, such as impact on cortisol reactivity (Miller et al, 2013) and the relationship between stress exposure and depression (Caspi et al, 2003; Karg et al, 2011), have required very large sample sizes to detect. However, other effects, such as amygdalar reactivity (Hariri and Weinberger, 2003), have required smaller samples. Because many effects on amygdalar function are sensitive to adrenergic manipulation at the beta receptors (Cahill et al, 1994), and effects of stress on these types of cognitive tasks are similarly sensitive (Alexander et al, 2007), smaller samples may be sufficient to be informative in this setting, at least on an exploratory basis. Moreover, the current study is facilitated by the statistical advantages of within-subject comparisons.

The small number of participants lacking a copy of the S-allele is consistent with published allele frequencies for the 5-HTTLPR (Wendland et al, 2006), but it limits any conclusions that can be drawn about the effect specifically within this group. Of course, this limitation could be overcome by Mendelian randomization prior to enrollment in future studies. Furthermore, future studies would need to include a range of other variants known to affect 5-HTT function (Frodl et al, 2008; Murphy et al, 2013). Our preliminary findings merely suggest the need to look further in this direction with confirmatory studies.

Despite these limitations, our results do begin to suggest that genetic susceptibility to stress may influence the effect of stress on cognitive task performance, particularly for unconstrained cognitive flexibility tasks requiring a high degree of flexibility of access to lexical-semantic networks. However, these findings can only be considered exploratory based on this sample. Confirmation is needed with a larger sample, given the frequent problems with reproducibility in such genetic studies.

Even if confirmation is achieved, alternative hypotheses must also be considered, such as difficulty among S-allele participants transitioning from the stress task to the problem-solving tasks, which could also be related to putative psychiatric effects of the S-allele. For example, anxiety and neuroticism, which have been reported to be affected by the S-allele (Domschke and Dannlowski, 2010; Sen et al, 2004), could influence performance by affecting the transition from the stressor to the problem-solving tasks. Monitoring biological markers of the effect of stress, and tracking subjective stress ratings, would be helpful in evaluating these competing hypotheses. Future studies will need to address these findings in a more comprehensive manner, exploring the neural mechanism underlying these effects and looking at the effects on divergent tasks associated with creative cognition in addition to the convergent task assessed in this study.

Larger studies would also be needed to allow commentary on more than just the effect within the pooled S-allele group, and to have a sufficient sample to explore effects of participants' gender. Stress reactivity is well known to be influenced by gender (Brummett et al, 2008; Cahill and van Stegeren, 2003), and age can also be an important factor (Mueller et al, 2011). Additionally, larger samples would be needed to account for cyclic variations in

hormonal status among women, which also affect stress reactivity (Gordon and Girdler, 2014).

Furthermore, future work would need to move beyond the S-allele, looking in a more comprehensive manner at the impact of multiple variants affecting *SLC6A4* expression, as mentioned above (Frodl et al, 2008; Murphy et al, 2013), as well as downstream effects (Iurescia et al, 2016). Larger studies could explore the combined effects of other genes known to influence stress reactivity. If confirmed, these findings may also have implications for conditions associated with increased stress response. Studies may be warranted in populations such as individuals with test anxiety (Faigel, 1991) or performance anxiety (Laverdue and Boulenger, 1991), or in patients acutely withdrawing from cocaine (Kelley et al, 2005, 2007).

Future work might also explore how factors such as variations in the 5-HTT protein that determine individual variability in stress reactivity affect other aspects of cognition known to be influenced by stress. Examples include the effects of stress on prefrontal processing and attentional control (Liston et al, 2009), other types of cognitive flexibility, such as goal shielding at the expense of cognitive flexibility (Plessow et al, 2011), flexible implementation of task goals (Plessow et al, 2012), and strategies of task-set reconfiguration in task shifting (Steinhauser et al, 2007), and even economic decision making (Porcelli and Delgado, 2009).

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Glossary

5-HTT	serotonin transporter
5-HTTLPR	promoter region of the serotonin transporter gene
HR	heart rate
L-allele	long allele
S-allele	short allele
SBP	systolic blood pressure
SLC6A4	serotonin transporter gene
TSST	Trier Social Stress Test

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FIGURE 1.

Sum of the natural logarithm of solution latencies for anagrams between conditions of stress and no stress (control) for participants with and without a copy of the S-allele. * $P < 0.05$.

TABLE 1

Performance on Cognitive Tasks Under Stress and Control (No Stress) Conditions, by S-Allele Carrier Status

Measure	S-Allele Carrier		L-Allele Homozygote	
	Control	Stress	Control	Stress
Anagrams (sum of natural log seconds to complete)	19.7 ± 2.02 *	21.7 ± 2.4 *	22.4 ± 3.2	20.9 ± 3.9
Grooved Pegboard (average seconds to complete)	64.2 ± 2.3	63.8 ± 1.9	71.9 ± 5.6	68.4 ± 8.0

Data are reported as mean ± standard error.

* S-allele Control condition significantly different from S-allele Stress condition for cognitive task (anagrams). $P = 0.032$.