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THE HIPPOCAMPAL RESPONSE TO PSYCHOSOCIAL STRESS VARIES WITH SALIVARY URIC ACID LEVEL

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Abstract—Uric acid is a naturally occurring, endogenous compound that impacts mental health. In particular, uric acid levels are associated with emotion-related psychopathology (e.g., anxiety and depression). Therefore, understanding uric acid's impact on the brain would provide valuable new knowledge regarding neural mechanisms that mediate the relationship between uric acid and mental health. Brain regions including the prefrontal cortex, amygdala, and hippocampus underlie stress reactivity and emotion regulation. Thus, uric acid may impact emotion by modifying the function of these brain regions. The present study used functional magnetic resonance imaging (fMRI) during a psychosocial stress task to investigate the relationship between baseline uric acid levels (in saliva) and brain function. Results demonstrate that activity within the bilateral hippocampal complex varied with uric acid concentrations. Specifically, activity within the hippocampus and surrounding cortex increased as a function of uric acid level. The current findings suggest that uric acid levels modulate stress-related hippocampal activity. Given that the hippocampus has been implicated in emotion regulation during psychosocial stress, the present findings offer a potential mechanism by which uric acid impacts mental health.

Key words: fMRI, emotion, uric acid, hippocampus.

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Abbreviations: AFNI, Analysis of Functional NeuroImages; ATP, adenosine triphosphate; BOLD, blood oxygen-level dependent; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; EPI, Echo-Planar imaging; fMRI, functional magnetic resonance imaging; FWE, family-wise error; HRF, hemodynamic response function; MTL, medial temporal lobe; PFC, prefrontal cortex; vmPFC, ventromedial prefrontal cortex.

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INTRODUCTION

Uric acid is an endogenous compound that is formed as the end-product of purine metabolism. Although imbalanced uric acid levels have a long-standing link with medical conditions such as gout, uric acid also affects the central nervous system. For example, increased uric acid levels accelerate purine transformation, leading to alterations of neural transmission (Ortiz et al., 2015; Ozten et al., 2015). Additionally, uric acid has been linked with neurodegenerative conditions, such as Alzheimer's, Parkinson's, and Huntington's disease, as well as Multiple Sclerosis and mild cognitive impairment (MCI) associated with aging (Bowman et al., 2010; Fang et al., 2013). The role of uric acid in mental health is also an emerging area of research. For example, uric acid levels are associated with emotion-related psychopathology, such as anxiety and mood disorders (Machado-Vieira et al., 2008; Lyngdoh et al., 2013; Jahangard et al., 2014; Kesebir et al., 2014; Albert et al., 2015). Within non-clinical populations, individuals with elevated uric acid levels are more likely to be impulsive (Sutin et al., 2014), hyperactive (Barrera et al., 1988; Johnson et al., 2011), and disinhibited (Lorenzi et al., 2010). Together, these findings provide converging evidence that uric acid may play an important role in psychological health. However, no study to date has examined the extent to which brain function varies with uric acid levels. Thus, the neural mechanisms that mediate uric acid's effect on mental health remain unclear. Determining whether emotion-related brain function varies with individual differences in uric acid levels will provide valuable insight into uric acid's influence on emotion-related neural systems.

Uric acid may play an important role in mental health by modulating the emotional response to stress. For example, the autonomic response (blood pressure) to acute stress varies as a function of baseline uric acid levels (Ohno et al., 2015). Low uric acid concentrations are also associated with anxiety and depression (Bove et al., 2010; Wen et al., 2012; Lyngdoh et al., 2013). Further, the social inhibition that characterizes certain stress, anxiety, and depressive disorders may be linked to low uric acid levels (Bove et al., 2010; Wen et al., 2012). Uric acid's role in social inhibition has also been previously demonstrated in treatment studies of bipolar disorder. Specifically, patients with bipolar disorder show higher uric acid levels during manic episodes (characterized by disinhibition), and therapeutic reductions in uric acid concentrations via allopurinol (a xanthine oxidase inhibitor)

significantly reduce manic symptoms (Machado-Vieira et al., 2008). Furthermore, the degree of uric acid reduction correlates with improvement in manic symptom severity (Jahangard et al., 2014). Even within non-clinical populations, baseline uric acid has been linked to psychosocial behavioral tendencies (Lorenzi et al., 2010; Sutin et al., 2014). For example, lower uric acid levels are associated with social inhibition (i.e., general social fearfulness and introverted tendencies), whereas higher uric acid levels are associated with impulsivity and excitement seeking (characterized by a tendency to seek crowded and stimulating environments) (Raina and Vats, 1982; Lara et al., 2008; Lorenzi et al., 2010; Sutin et al., 2014). Although these findings suggest uric acid plays a modulatory role in psychosocial behavior and stress reactivity, the neural mechanisms that underlie these associations are not well understood.

Prior neuroimaging investigations of psychosocial stress suggest neural activity within the prefrontal cortex (PFC) and medial temporal lobe (MTL) support important aspects of the stress response. Specifically, the dorsolateral prefrontal cortex (dlPFC), dorsomedial prefrontal cortex (dmPFC), ventromedial prefrontal cortex (vmPFC), amygdala, and hippocampal complex (i.e., hippocampus and surrounding cortex) mediate psychosocial stress reactivity (Pruessner et al., 2008; Dedovic et al., 2009a; Khalili-Mahani et al., 2010). This prior work indicates that neural activity within these brain regions varies with stress-elicited glucocorticoid release. Thus, recruitment of the prefrontal cortex and MTL suggests that brain regions responsible for emotion expression and regulation mediate the response to psychosocial stress (Pruessner et al., 2008).

The current study examined the relationship between inter-subject variations in extant salivary uric acid levels and blood-oxygen-level dependent (BOLD) functional magnetic resonance imaging (fMRI) during a psychosocial stress task (Montreal Imaging Stress Task; MIST) (Dedovic et al., 2005). Salivary uric acid was measured in the current study as a non-invasive alternative to serum uric acid measurement, which requires a blood draw. We hypothesized that stress-elicited brain activity would vary with individual differences in existing (i.e., baseline) uric acid levels given (1) that uric acid affects neural transmission (Ortiz et al., 2015; Ozten et al., 2015) and (2) the link between uric acid and psychosocial stress (Bove et al., 2010; Lorenzi et al., 2010; Lyngdoh et al., 2013; Sutin et al., 2014). Specifically, we expected the BOLD signal response within the PFC and MTL, to vary with uric acid level. Thus, the present study provides a novel assessment of emotion-related brain function that may mediate the impact of uric acid on mental health.

EXPERIMENTAL PROCEDURES

Participants

55 right-handed volunteers (33 males, 22 females, mean age = 19.58 years, age range 18–21 years) participated in an fMRI study using a variation of the MIST. Data from one participant were excluded because the uric acid concentration fell 3 standard deviations above the mean. Remaining participants fell within the approximate range (0.5–7.5 mg/dL) for salivary uric acid previously reported in non-clinical samples (Shibasaki et al., 2012; Soukup et al., 2012). Three additional participants were excluded due to data acquisition errors that prevented synchronization of stimulus presentations to imaging data. Thus, 51 participants (29 males, 22 females, mean age = 19.55 years, age range 18–21 years) were included in the final analysis. All participants provided written informed consent as approved by the University of Alabama at Birmingham Institutional Review Board.

Task design

Participants were familiarized with the MIST by completing a computer-administered set of practice math problems prior to entering the scanning environment. Following practice, participants completed a modified version of the MIST during BOLD Echo-Planar imaging (EPI). Two separate scans assessed Stress and Control conditions of the task. Each of these scans contained 54 trials and lasted approximately 8 min (Fig. 1). Trials were six seconds in duration and were separated by a variable inter-trial interval (1–3 s). Each trial consisted of a response window followed by rest and visual feedback. During the response window, a unique math problem (e.g., "6 + 3 – 1 = ?") and digit choices (range: 0–9) appeared on the screen. Participants used an MR compatible joystick (Current

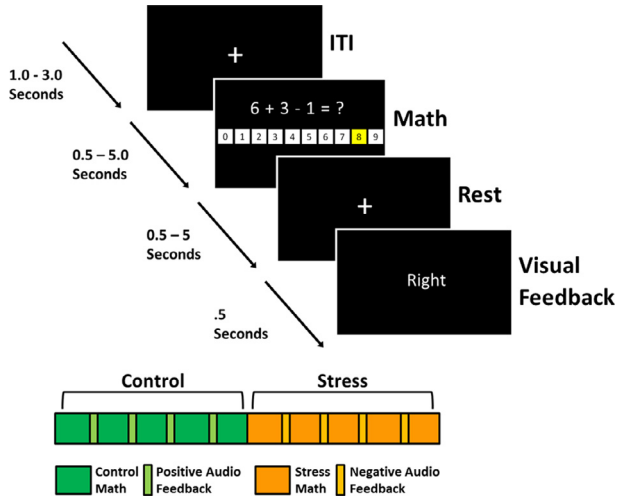

Fig. 1. Trial and task progressions. Top panel: Each trial lasted six seconds and consisted of a unique math problem, response window, rest, and visual feedback. Responses were made by highlighting digits (1–9) using an MR compatible joystick. Bottom Panel: Experimental sessions began with the Control version of the MIST, presented under low stress conditions. Participants then completed the Stress version of the MIST, presented under high stress conditions. Green rectangles represent periods of time when participants completed math problems during the Control MIST. Periodically, positive auditory feedback was presented to participants (light green rectangles). Likewise, orange rectangles represent the periods of time when participants completed math problems during the Stress MIST. The light orange rectangles represent periodic negative auditory feedback. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)