



Genetic associations with performance on a behavioral measure of distress intolerance

Ananda B. Amstadter^{a,*}, Stacey B. Daughters^b, Laura MacPherson^b, Elizabeth K. Reynolds^c,
Carla Kmett Danielson^d, Frances Wang^e, Marc N. Potenza^f, Joel Gelernter^g, C.W. Lejuez^b

^a Virginia Commonwealth University, USA

^b University of Maryland–College Park, USA

^c University of Maryland–College Park and Brown Medical School, USA

^d Medical University of South Carolina, USA

^e Arizona State University, USA

^f Yale University, USA

^g Yale University School of Medicine, USA

ARTICLE INFO

Article history:

Received 23 June 2011

Received in revised form

11 September 2011

Accepted 29 September 2011

Keywords:

COMT

5-HTTLPR

Distress tolerance

ABSTRACT

Both theory and empirical evidence support possible associations between two candidate genetic polymorphisms (*SLC6A4* 5-HTTLPR l/s and *COMT* Val¹⁵⁸Met – rs4680 variants) and emotion-regulation difficulties. One particular form of emotion-regulation difficulty, distress intolerance, has been measured using a behavioral assessment in youth; data indicate a relationship with poor psychological functioning. No prior study has investigated genetic influences on emotion-regulation difficulties in youth. As part of a larger longitudinal study on adolescent risk behaviors, 218 10–14 year-old youths from the metropolitan Washington, D.C., area completed a measure of distress intolerance, the Behavioral Indicator of Resilience to Distress (BIRD), and provided saliva samples for DNA extraction and genotyping. Results indicate that those with one or two copies of the s allele of the 5-HTTLPR polymorphism were more likely to perform poorly on the task (i.e., choose to quit) than were those homozygous for the l allele. Participants who were Val allele carriers of the *COMT* Val¹⁵⁸Met polymorphism were also more likely to quit the task compared to Met homozygotes. A summative risk allele score was created to combine the two polymorphisms, and each risk allele was associated with a 1.75 fold increased likelihood of quitting the task. Exploratory analyses revealed that emotional abuse moderated the relationship between the 5-HTTLPR and BIRD performance, as well as the genetic risk allele and the BIRD. This is the first investigation of genetic predictors of a behavioral measure of tolerance to distress. Results suggest that distress tolerance is at least partially regulated by specific genetic variants. Implications are discussed.

© 2011 Elsevier Ltd. All rights reserved.

Distress intolerance, which is defined as limited persistence in goal-directed activity when experiencing aversive emotional states (Brown et al., 2005), is a key component of emotion regulation, and is associated with internalizing and externalizing psychopathology. Adults with distress intolerance evidence increased rates of Axis II psychopathology (Daughters et al., 2008; Gratz et al., 2006), and eating disorders (Anestis et al., 2007), as well as greater substance abuse severity (Quinn et al., 1996) and more frequent relapse

during abstinence attempts (Brown et al., 2002; Daughters et al., 2005). Recent study of adolescent populations indicate that distress intolerance is associated with externalizing and internalizing features that contribute to the development of future psychopathology such as anxiety and depressive symptoms, delinquent behavior and substance use (Daughters et al., 2009), risk-taking behaviors (MacPherson et al., 2010), and self-harm (Nock and Mendes, 2008). Distress tolerance may also be related to traumatic stress and related phenotypes in certain populations (Danielson et al., 2010).

The distress intolerance construct originates with negative reinforcement theory, suggesting that the motivational basis of many maladaptive behaviors is the escape or avoidance of affective distress (Baker et al., 2004; Metcalfe and Mischel, 1999). For

* Corresponding author. Virginia Institute of Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Department of Psychiatry, 800 E. Leigh Street, PO Box 980126, Richmond, VA 23298-0126, USA. Tel.: +804 828 8800; fax: +804 828 8801.

E-mail address: abamstadter@vcu.edu (A.B. Amstadter).

instance, when an individual is presented with a significant stressor that results in affective distress (e.g., anxiety), the individual in turn narrows his/her focus on this experience. As such, escaping (and over time, avoiding) this affective state becomes a primary motivational concern. Using substance dependence as an example, an individual in the early stages of an abstinence attempt who is experiencing physical and psychological withdrawal symptoms such as irritability and anxiety may turn to substances to relieve these symptoms, thereby continuing the cycle of addiction. The distress intolerance paradigm was developed to assess this process quantitatively, and involves participant engagement in, and persistence on, a computerized task that gradually increases in difficulty, thereby increasing affective distress. The participant has the option to persist (with some small positive reinforcement available for persisting) or to terminate the task, thereby reducing affective distress in the short-term and rewards in the long-term. From this perspective, the measurement of distress intolerance effectively creates a laboratory paradigm with high internal validity by creating a synthetic controlled situation where affective distress and negative reinforcement processes interact, allowing the participant to make the real-world decision of persisting through or avoiding distress.

The genetic mechanisms underlying the development of distress intolerance are relatively poorly understood. This limited understanding represents a gap in the literature as the discovery of genetic predispositions for the development of distress intolerance may aid in the early identification of at-risk individuals. Of particular interest, findings indicate that alleles at both the promoter region of the serotonin transporter gene (*SLC6A4*) and *COMT* Val¹⁵⁸Met (rs4680) may be risk factors for emotion-regulation difficulties. Pre-clinical data show evidence for large increases in serotonin (5-HT) efflux in the medial pre-frontal cortex in response to uncontrollable, but not controllable, stress in humans (Bland et al., 2003). Additionally, serotonin is implicated in amygdala inhibition (Rainnie, 1999; Rainnie et al., 1991). Anxiety has been found to be inversely related to 5-HT efflux in animal models (Hashimoto et al., 1999). Therefore, examinations of genetic variants that functionally are related to 5-HT activity may be related to stress regulation constructs, such as distress tolerance. The biological activity of 5-HT is regulated by the protein product of the *SLC6A4* gene, with the serotonin transporter influencing synaptic availability of 5-HT by sequestering it back into presynaptic neurons. A variable number tandem repeat (VNTR) polymorphism within the *SLC6A4* gene, referred to as the 5-HTTLPR polymorphism, has two alleles – short (s) and long (l). As compared to carriers of the s variant, carriers of the l of the 5-HTTLPR polymorphism transcribe upwards of two times as much mRNA encoding the 5-HT transporter (5-HTT), and when examining protein levels from membrane preparations from lymphoblasts, l homozygotes had 30–40% higher marker binding compared to the membranes from l/s or s/s cells (Lesch et al., 1996). This reduced 5-HTT transcription of the s allele presumably results in less efficient reuptake and increased levels of synaptic serotonin (Lesch et al., 1996). Converging lines of evidence suggest that the 5-HTTLPR s allele is related to multiple behavioral and neural constructs that share an underlying aspect of negative affect reactivity and regulation, therefore having clear relevance to distress tolerance. For example, in human studies, the s allele has been associated with anxiety and stress related phenotypes. Specifically, the s allele of polymorphism has been associated with greater amygdala responding to fearful faces and other forms of threatening emotional stimuli (Hariri et al., 2002; Munafò et al., 2008). In fact, this locus has been found in a meta-analysis to account for up to 10% of the variance in amygdala reactivity to threatening stimuli (Munafò et al., 2008), underscoring the importance of studying this

locus in relation to a behavioral manifestation of tolerance of negative emotion (i.e., distress tolerance). Carriers of the s allele also show decoupling of the amygdala-frontal brain feedback circuit responsible for extinction of fear conditioning (Pezawas et al., 2005). Also relevant to distress tolerance, the s allele has been associated with prolonged cortisol secretion in response to an acute stressor (Gotlib et al., 2008). Taken together, it is possible that stress related increases in 5-HT may be compounded in s' allele carriers, as they already have elevated synaptic 5-HT, and following, the s' allele carriers may have poorer distress tolerance.

The *COMT* enzyme catalyzes the transfer of a methyl group from S-adenosyl-methionine to a hydroxyl group of catecholamines and therefore is involved in the degradation of pre-frontal cortex catecholamines (e.g., dopamine, epinephrine, and norepinephrine; Weinshilboum et al., 1999). Given the key role catecholamines play in emotion related phenotypes, there is reason to believe that functional variants within the *COMT* gene may be related to distress tolerance. *COMT* Val¹⁵⁸Met (rs4680) is a functional polymorphism influencing dopaminergic systems. It involves a common valine (Val; high activity) to methionine (Met; low activity) transition that has been associated with a 3–4 fold difference in *COMT* enzyme activity between homozygotes (Val/Val vs. Met/Met), with heterozygotes showing intermediary enzyme activity (Weinshilboum et al., 1999).

This polymorphism is a clear candidate for studying in relation to distress tolerance as it has been found to be associated with constructs that are related to distress tolerance (e.g., neural activity to negative stimuli, emotionality during stress); however, there is mixed evidence as to which allele (Met or Val) is associated with these emotion regulation-related phenotypes. Low distress tolerance is related to anxiety disorders (Daughters et al., 2009), and the Met allele of this polymorphism has been found to be associated with anxiety disorders (Domschke et al., 2004; Enoch et al., 2003; McGrath et al., 2004; Olsson et al., 2005; Pooley et al., 2007; Woo et al., 2004). The Met allele has also been associated with other constructs related to distress tolerance, such as greater pain sensitivity (Diatchenko et al., 2005), and a potentiated startle reflex to aversive stimuli (Montag et al., 2008). Of relevance to the present study of distress tolerance, in a sub-sample of adolescent girls, homozygous Val-allele carriers reported greater maintenance of positive emotions during stress compared to Met¹⁵⁸ homozygotes (Vaughn et al., 2009). Converging lines of evidence suggest that the Met allele may be related to poorer distress tolerance; however, discrepant findings of this polymorphism have been reported in the literature, and a case could also be made for the Val allele being associated with poorer distress tolerance. For example, the Val carriers have been shown to perform poorer than Met carriers on tasks that are pre-frontal cortex dependent, such as the Wisconsin Card Sorting Test (Egan et al., 2001), and Val carriers also display relatively greater activation of the dorsolateral pre-frontal cortex (PFC) during the Wisconsin Card Sorting Task performance, suggesting that Val carriers have less efficient PFC function (cf., Tunbridge et al., 2006), which may also be related to poor emotion regulation.

Taken together, the link between distress intolerance and a variety of important clinical outcomes suggests it may provide an important intermediary phenotype for putative genetic markers having similar clinical associations. In the current study, we address the first step in this line of research by examining whether adolescents who demonstrate diminished persistence during a stressful task (i.e., distress-intolerant youth) are more likely to carry the s allele of the 5-HTTLPR. We also hypothesize a relationship between performance on the task and the *COMT* Val¹⁵⁸Met (rs4680) polymorphism, with distress-intolerant youth being more likely to carry the Met allele, as previous research has found that

متن کامل مقاله

دریافت فوری ←

ISIArticles

مرجع مقالات تخصصی ایران

- ✓ امکان دانلود نسخه تمام متن مقالات انگلیسی
- ✓ امکان دانلود نسخه ترجمه شده مقالات
- ✓ پذیرش سفارش ترجمه تخصصی
- ✓ امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
- ✓ امکان دانلود رایگان ۲ صفحه اول هر مقاله
- ✓ امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
- ✓ دانلود فوری مقاله پس از پرداخت آنلاین
- ✓ پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات