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The relation between GAD1 and PTSD symptoms: Shared risk for depressive symptoms

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To the Editors

Posttraumatic stress disorder (PTSD) and major depressive disorder (MDD) have substantial public impact and are common outcomes following trauma exposure. Thus, great interest exists in determining individual difference factors associated with greater risk for these outcomes. Both PTSD and MDD are at least moderately heritable and twin studies have demonstrated a high degree of overlap (Koenen et al., 2008). However, a clear understanding of which specific variants (e.g., single nucleotide polymorphisms [SNPs]) confer risk for both disorders has been elusive.

Recent research suggests that genetic variation of the glutamate and γ -aminobutyric acid (GABA) system genes may be useful for understanding the genetic underpinnings of both disorders. Glu and GABA mediate the high majority of excitatory and inhibitory transmissions, and their interaction is thought to influence cognition and emotion (Sanacora et al., 2012). An enzyme of interest within this system is glutamic acid decarboxylase (GAD1), which converts glutamate to GABA. The GAD system influences mood stability and the pathophysiology of mood and anxiety disorders (Sanacora et al., 2012). To date, *GAD1* genetic variants have been associated with mood disturbance (Lundorf et al., 2005) and panic disorder (Weber et al., 2012). Thus, *GAD1* SNPs may impact both mood and anxiety-like traits, and may also be relevant following stress or trauma exposure in influencing risk for PTSD as well as depression.

Given this preliminary work, we explored whether a genetic risk sum score (GRSS) capturing risk for *GAD1* is significantly associated with PTSD symptoms. We also tested whether this GRSS is associated with depressive symptoms. These effects were examined over and above the covariates age, sex, and race.

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We tested these associations in a sample of 513 combat Veterans, recruited through the Cincinnati Veterans Affairs Medical Center (VAMC) and Charleston VAMC. Participants were eligible for inclusion if they had combat exposure, and did not meet criteria for lifetime DSM-IV schizophrenia, bipolar disorder, or active substance abuse/dependence in the past six months. Individuals with combat exposure and PTSD were considered cases and individuals with combat exposure but no PTSD were considered controls. A total of 513 individuals (age 21–80) enrolled in the study, with 82.8% male and 69% Caucasian (with 24.2% African-American and 6.8% Other). To assess PTSD and depressive symptoms, the Structured Clinical Interview for DSM-IV (SCID), Mini-International Neuropsychiatric Interview (MINI), Hamilton Depression Scale (HAM-D) and the Clinician Administered PTSD Scale (CAPS) were used.¹

Genomic DNA was extracted from blood samples using a Wizard Genomic DNA purification kit (Promega, Madison, WI) using the manufacturer's protocol. SNPs with call rates ($< 95\%$) and deviations from Hardy-Weinberg equilibrium ($p < 10^{-6}$) were eliminated. Initially 12 *GADI* SNPs, thought to be representative of the entire *GADI* gene, were genotyped. Of these 12 SNPs, 10 remained after pruning for linkage disequilibrium² (LD; i.e., $r^2 > .7$). These 10 SNPs were used in the creation of this GRSS, employing an additive coding scheme (i.e., score of 0–2 for each SNP added together).

In order to test the hypothesized effects, a path model was estimated using MPlus Version 7). Age, sex, and race were used as covariates. The associations between the GRSS and PTSD symptoms and depression symptoms were tested. Interactions among covariates and these three constructs (e.g., sex X *GADI*) were initially estimated, and non-significant interactions ($p < .05$) were trimmed.

The final model showed good fit to the data: The Root Mean Square Error of Approximation (RMSEA)=.068, Comparative Fit Index (CFI)=.918, Standardized Root Mean Square Residual (SRMR)=.037. African-Americans reported more symptoms than Caucasians ($B=.150$, $p < .001$), who reported more symptoms than those who identified as Other ($B=-.170$, $p < .05$). Finally, greater genetic risk was associated with more PTSD symptoms ($B=.051$, $p < .001$). No interactions were significant.

¹Across the entire sample, 83.9% ($n=430$) endorsed any PTSD symptoms (65.1%, $n=334$ met criteria for PTSD) and 92.6% ($n=475$) endorsed any depression symptoms (42.7%, $n=219$ met criteria for depression). Among subgroups, these numbers change somewhat. Specifically, among males: 86.9%/ $n=369$ endorsed any PTSD symptoms and 92%/ $n=391$ endorsed any depression symptoms (67%/ $n=285$ met criteria for PTSD; 45%/ $n=190$ met criteria for depression); among females 69.4%/ $n=61$ endorsed any PTSD symptoms and 96.7%/ $n=85$ endorsed any depression symptoms (56%/ $n=235$ met criteria for PTSD; 33%/ $n=29$ met criteria for depression).

Additionally, among Caucasians: 92.5%/ $n=115$ endorsed any PTSD symptoms and 94.5%/ $n=117$ endorsed any depressive symptoms (78.2%/ $n=97$ met criteria for PTSD; 46.8%/ $n=58$ met criteria for depression), among African-Americans: 74.3%/ $n=26$ endorsed any PTSD symptoms and 89.5%/ $n=31$ endorsed any depressive symptoms (48.6%/ $n=17$ met criteria for PTSD; 42.9%/ $n=15$ met criteria for depression), and among those identifying as Other: 81.8%/ $n=290$ endorsed any PTSD symptoms and 91.9%/ $n=325$ endorsed any depressive symptoms (62.1%/ $n=220$ met criteria for PTSD; 41.2%/ $n=146$ met criteria for depression). Finally, among the youngest third of participants (age 21–33) 91.3%/ $n=162$ endorsed any PTSD symptoms and 92.9%/ $n=164$ endorsed any depressive symptoms (68.4%/ $n=121$ met criteria for PTSD; 48.6%/ $n=86$ met criteria for depression), among the middle third of participants (age 34–50) 79.6%/ $n=131$ endorsed any PTSD symptoms and 95.8%/ $n=158$ endorsed any depressive symptoms (57.6%/ $n=95$ met criteria for PTSD; 37%/ $n=61$ met criteria for depression), and among the oldest third of participants (age 51–80) 80.2%/ $n=137$ endorsed any PTSD symptoms and 90%/ $n=154$ endorsed any depressive symptoms (69%/ $n=118$ met criteria for PTSD; 42.1%/ $n=72$ met criteria for depression).

²These 10 SNPs are: rs2241165, rs3791850, rs1420385, rs3791878, rs4667662, rs3791858, rs4297845, rs6755814, rs1978340, and rs701492.

In terms of effects on depressive symptoms, African-Americans reported more symptoms than Caucasians ($B=.125$, $p < .01$). Additionally, genetic risk was associated with depressive symptoms ($B=.094$, $p=.001$).³ No interactions were significant.

These findings are in line with work suggesting that *GADI* may influence mood stability and anxiety (Sanacora et al., 2012; Lundorf et al., 2005). It may be that individuals at higher risk on *GADI* SNPs have difficulty converting glutamate to GABA, which has anxiolytic properties (Zwanzger and Rupprecht, 2005). Following a trauma, individuals at higher genetic risk on *GADI* may experience physiological effects of anxiety, overconsolidation of the fear memory, and negative thoughts about the event, decreasing their ability to extinguish fear responses when reminded of the trauma and increasing the likelihood of mood-related disturbances. Individuals at higher genetic risk on *GADI* may thus show increased PTSD and depressive symptoms. More work is needed to discern the functional properties of these SNPs in conferring risk for these two phenotypes.

Limitations should be considered when interpreting the results from this study. First, this study was only able to include 10 SNPs within *GADI*, so this risk score may be under-explaining variance in our phenotypes. Also, for a score using measured genes, our sample size was small, thus we may have been under-powered to detect genetic effects, as well as potential interactions between *GADI* genetic variants and covariates. Finally, although findings held in a subsample of only Caucasians, population stratification may have occurred.

Despite these limitations, the current study extends previous research by finding that variation in *GADI* is one mechanism by which individuals may come to develop increased PTSD symptoms following trauma. These findings also indicate that *GADI* may represent a shared genetic risk factor for PTSD and depression. Findings implicate SNPs within *GADI* in mood regulation and physiological effects of anxiety following exposure to a trauma, and thus, risk for depression and PTSD. Given the paucity of work examining the link between *GADI* SNPs and these phenotypes, this work is incredibly important, as it provides initial insight into SNPs that account for the shared genetic overlap in depression and PTSD.

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References

- Koenen KC, Fu QJ, Ertel K, Lyons MJ, Eisen SA, True WR, Goldberg J, Tsuang MT. Common genetic liability to major depression and posttraumatic stress disorder in men. *J Affect Disord.* 2008; 105:109–115. [PubMed: 17540456]
- Lundorf MD, Buttenschon HN, Foldager L, Blackwood DHR, Muir WJ, Murray V, et al. Mutational screening and association of glutamate decarboxylase 1 as a candidate susceptibility gene for

³The effects of the GRSS on PTSD and depressive symptoms also held when analyses were limited to Caucasians.

bipolar affective disorder and schizophrenia. *Am J Med Genet.* 2005; 135B:94–101. [PubMed: 15806582]

Sanacora G, Treccani G, Popoli M. Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. *Neuropharmacology.* 2012; 62:63–77. [PubMed: 21827775]

Weber H, Scholz CJ, Domschke K, Baumann C, Klauke B, Jacob CP, et al. Gender differences in associations of glutamate decarboxylase 1 gene (GAD1) variants with panic disorder. *PLoS One.* 2012; 7:e37651–e37658. [PubMed: 22662185]

Zwanzger P, Rupprecht R. Selective GABAergic treatment for panic? Investigations in experimental panic induction and panic disorder. *J Psychiatry Neurosci.* 2005; 30:167–175. [PubMed: 15944741]