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Ventromedial and insular cortical volume moderates the relationship between *BDNF* Val66Met and threat sensitivity

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Abstract

While the BDNF Val66Met polymorphism has been linked to various trauma and anxiety – related psychiatric disorders, limited focus has been on the neural structures that might modulate its relationship with objective measures of threat sensitivity. Therefore, we assessed whether there was an interaction of Val66Met polymorphism with brain area volumes previously associated with anxiety and PTSD, such as the ventromedial prefrontal cortex (vmPFC), insular cortex

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(IC), and dorsal and ventral anterior cingulate cortices (dACC and vACC), in predicting fear-potentiated psychophysiological response in a clinical sample of Veterans. 110 participants engaged in a fear-potentiated acoustic startle paradigm and provided genetic and imaging data. Fear conditions included no, ambiguous, and high threat conditions (shock). Psychophysiological response measures included electromyogram (EMG), skin conductance response (SCR), and heart rate (HR). PTSD status, trauma history, and demographics were also assessed. There was an interaction of Met allele carrier status with vmPFC, IC, dACC, and vACC volumes for predicting SCR ($p < 0.001$ for all regions). However, only vmPFC and IC significantly moderated the relationship between Val66Met and psychophysiological response (SCR). The Val66met polymorphism may increase susceptibility to PTSD and anxiety disorders via an interaction with reduced vmPFC and IC volume. Future research should examine whether these relationships might be associated with a differential course of illness longitudinally or response to treatments.

Keywords

1. Introduction

Etiological models of anxiety and fear-related disorders such as Posttraumatic Stress Disorder (PTSD) stem from an understanding of the confluence of external toxic factors against the backdrop of internal, predispositional vulnerabilities (Mineka and Oehlberg, 2008). PTSD in particular provides an unfortunate natural experiment that highlights how population diversity might play a role in symptom severity subsequent to trauma exposure. The large disparity between population-wide trauma exposure and PTSD cases reinforces the need to better understand the neurobiological and genetic factors that may affect PTSD susceptibility (Kilpatrick et al., 2007; McCall-Hosenfeld et al., 2014; Yehuda et al., 2015).

Consistent findings have implicated prefrontal and cingulate structures in the maintenance of PTSD-related arousal (Fenster et al., 2018; Milad and Quirk, 2012). Findings suggest structural and functional deficits in the ventromedial prefrontal cortex (vmPFC) are associated with greater levels of arousal in individuals with PTSD and individuals with PTSD exhibit vmPFC hypofunction and elevated amygdala activity (Admon et al., 2013; Etkin and Wager, 2007). Other studies indicate individuals with PTSD have both reduced volume and increased activation of the dorsal anterior cingulate and insular cortices (dACC and IC respectively (Akiki et al., 2017);). The IC in particular plays a complex role as IC neuronal engagement occurs during the anticipation of aversive stimuli (Simmons et al., 2006, 2011) where individuals with PTSD and anxiety disorders engage in greater insular recruitment when exposed to threatening and aversive stimuli (Bruce et al., 2013; Simmons et al., 2013). These neurobiological findings are likely influenced by genetic mechanisms. Therefore, examining certain polymorphisms that govern learning at a molecular level may aid in our understanding of how cortical abnormalities influence threat reactivity and arousal.

Brain derived neurotrophic factor (BDNF) is a widely expressed neurotrophin in the mammalian central nervous system (CNS) and due to its mediating role in long-term potentiation (LTP) and synaptic plasticity, it is critical for neural development. Earlier research indicate that BDNF enhances presynaptic neurotransmitter vesicle docking activity and facilitating N-methyl-D-aspartate (NMDA) receptor action in postsynaptic neurons (Jovanovic et al., 2000; Yamada et al., 2002). More recently, interest has focused on *BDNF* Val66Met, a common single nucleotide polymorphism (SNP) that results in a substitution of methionine (Met) for valine (Val) at codon 66 in the pro-domain of the human BDNF protein, in its role in stress and anxiety disorders (Bruenig et al., 2016). Evidence suggests that the Met substitution results in impaired BDNF intercellular packaging and secretion regulation resulting in lower cerebral BDNF levels, which in turn adversely affects cortically driven fear memory extinction via deficits in LTP (Bekinschtein et al., 2014; Egan et al., 2003). This would suggest that Met allele are more reactive to perceived threat due to LTP related extinction deficits, which in turn would increase susceptibility to fear-related psychiatric disorders (Andero and Ressler, 2012). Research using Met knock-in mice corroborates this hypothesis where Met mice exhibited an impairment in contextual fear learning and reduced BDNF secretion levels, which were partially rescued with BDNF infusions (Liu et al., 2004). Furthermore, recent findings by our group and others have shown that Met allele carriers, particularly those with PTSD, exhibit greater threat reactivity compared to non-Met allele carriers (Mühlberger et al., 2014; Young et al., 2018b; Zhang et al., 2014, 2016).

It is suspected that the Val66Met – fear based learning relationship may be modulated by abnormalities in neurological structure and function. Earlier findings suggest that the Met allele is linked to smaller vmPFC volume and less vmPFC dendritic complexity, which in turn is associated with extinction learning deficits (Yu et al., 2009). Moreover, the Met allele may be associated with limbic system-mediated (e.g. amygdala, hippocampus) deficits in stress response in both animal and human samples (Notaras et al., 2016; Perez-Rodriguez et al., 2017). Moreover, human Met allele carriers exhibit greater activation in areas associated with the fear network (e.g. insula and amygdala) and less activation in prefrontal areas such as the vmPFC and subgenual ACC during acquisition and extinction phases of fear conditioning respectively (Lonsdorf et al., 2015; Soliman et al., 2010). While these studies have illuminated the neuropathological mechanisms that underlie the Val66Met stress-response system relationship, few studies have attempted to examine the above factors in clinical populations within the context of trauma exposure and PTSD. Therefore, using neurostructural imaging data, the current study aimed to extend previous findings by examining how the vmPFC, ACC (both dACC and vACC), and IC, might modulate the relationship between Val66Met on both threat sensitivity and physiological arousal in a fear-potentiated startle paradigm. We hypothesized that Met allele carriers with smaller vmPFC, ACC, or IC volumes would exhibit greater threat sensitivity as evidenced by larger inter-trial psychophysiological response magnitudes and exhibit elevated arousal as evidenced by greater psychophysiological response magnitudes over the three threat conditions all while controlling for PTSD status.

2. Methods and materials

2.1. Participants

We conducted secondary data analyses on Veterans from a cross-sectional study of the effects of Gulf War deployment on the brain. Gulf War Veterans were recruited between 2002 and 2007 as described previously (Apfel et al., 2011). Of the 369 Veterans from the original sample, 266 of them provided blood samples from which we extracted and analyzed DNA, 244 engaged in the psychophysiological response task, and 172 provided imaging data. Out of those, we had genetic, imaging, and psychophysiological task data from 169 Veterans. 112 Veterans were Val-Val carriers, 51 were Val-Met carriers, and 10 were homozygous Met-Met carriers. The sample conformed to the Hardy-Weinberg equilibrium ($\chi^2 = 0.11$; $p = 0.74$) and there were no significant differences between the minor allele frequencies of the three most representative races in our sample regarding this particular SNP ($\chi^2 = 0.26$; $p = 0.61$; National Institutes of Health HapMap Project, Bethesda MD).

Participants' demographic information and PTSD diagnosis were recorded for use in subsequent analyses based upon prior literature linking them to traumatic stress response (Neylan et al., 2005). Current PTSD diagnosis (i.e., within the past month) was evaluated by a Ph.D. level clinical interviewer using the Clinician Administered PTSD Scale (CAPS (Blake et al., 1995);). Participants were diagnosed with PTSD based upon frequency and severity of their CAPS scores (i.e. the "1, 2" rule; for a review, see (Blake et al., 2000). The vast majority of adult trauma exposure was combat-related. The last six items of the Trauma History Questionnaire, which focus on childhood physical and sexual abuse, were used to assess childhood abuse (Green, 1996). This investigation was carried out in accordance with the latest version of the Declaration of Helsinki, the study design was approved by both the Veterans Affairs and UCSF IRB committee, and informed consent was obtained after the nature of the procedures had been fully explained to all participants.

2.2. Psychophysiological response procedure

Electromyogram (EMG), skin conductance response (SCR), and heart rate (HR) were collected by trained technicians blind to participants' clinical status to assess psychophysiological response patterns to acoustic startle stimuli across no, ambiguous, and high threat conditions of electric shock over five trials for each of the threat conditions. Details of the psychophysiological response procedure are described in detail elsewhere (Young et al., 2018a, 2019) and provided as supplemental material to this manuscript.

2.3. Genotyping

Genomic DNA was extracted using the Promega Wizard Genomic DNA Purification Kit (Promega Biosystems, Sunnyvale, CA, USA). Samples were genotyped at the University of California, San Francisco Genomics Core Facility, using the ABI 3730xl (Applied Biosystems Inc., Foster City, CA, USA). Sequencer DNA Sequence Analysis Software (Gene Codes Corporation, Ann Arbor, MI) was used to analyze the Val66Met alleles.

2.4. Image acquisition and processing

Subjects were scanned on a 1.5 T Vision, Siemens MRI scanner (Siemens Medical Systems, Iselin, New Jersey). A T1-weighted 3D volumetric magnetization-prepared rapid gradient echo (MPRAGE) sequence was acquired with the following parameters: repetition time/ spin-echo time/inversion time = 10/4/300 ms, 1 mm × 1 mm in-plane resolution, and 1.5-mm slab thickness, angulated per-pendicular to the long axis of the vmPFC, IC, vACC, and dACC. FreeFreesufer version 4.5 http://surfer.nmr.mgh.harvard.edu) was used to estimate each subject's left and right volumes of their vmPFC, ACC, and IC along with their intracranial volume as previously described in (Chao et al., 2014). Total vmPFC volume, using FreeSurfer terminology, was defined by the sum of the left and right lateral and medial orbitofrontal cortices and is consistent with previous approaches (Boes et al., 2008; Desikan et al., 2006; Morey et al., 2016).

2.5. Data analyses

Based upon previous research concerning Val66Met (Armbruster et al., 2016; Marusak et al., 2016; Mühlberger et al., 2014), a dominant (versus recessive) genetic model was used where we combined both val-met and met-met carriers and compared them to val-val carriers in all analyses of this study. Due to non-normal distribution, vmPFC, IC, vACC, and dACC volumes were log transformed and entered as continuous variables in all models. Psychophysiological response outcome was assessed by using within-trial square root post-minus pre-EMG, SCR, and HR responses. Repeated measures linear mixed models were used to assess all interactions between Val66Met and vmPFC, Val66Met and IC, Val66Met and vACC, and Val66Met and dACC volumes on psychophysiological response (McCulloch and Neuhaus, 2001). Each model included Val66Met × structure volume × threat condition interaction terms. Demographic bivariate relationships on Val66Met (age, race (white vs. non-white), sex (female vs. male), education (in years), intracranial volume, Gulf War Illness status (Fukuda et al., 1998), and PTSD status were included in subsequent analyses if significant at p 0.10 (see Table 1.). Stata 15.1 was used to analyze the data (StataCorp LP, College Station, TX). Cohen's f^2 was used to assess proportion of model variance explained. f^2 was generated using user written code based on previously published methods described elsewhere (Selya et al., 2012). We calculated the interaction between neurostructural volume and Val66Met with respect to its between trial and threat condition changes in slope of psychophysiological response magnitude to examine within model slope change, where EMG, SCR, or HR magnitude = m and threat condition = t; thus, in standard notation, $m'(t) \approx 1/h\,[m(t+h) - m(t)]$.

3. Results

Demographic relationships to the Val66Met SNP are described in Table 1. Our sample was predominantly White and male with a mean age of approximately 46. Approximately 63% of participants reported trauma exposure and approximately 24% had PTSD (see Table 1.). The relationship between Val66Met and PTSD met the threshold for significance and therefore was included in subsequent mixed models as a covariate ($\chi^2 = 4.03$; $p < 0.072$).

3.1. Val66Met by vmPFC interactions on psychophysiological response

Overall model effects were significant for EMG, SCR, and HR repeated measures mixed models (*Wald* $\chi^2 = 128.05$; $p < 0.001$; *Wald* $\chi^2 = 120.13$; $p < 0.001$; and *Wald* $\chi^2 = 54.47$; $p < 0.001$). Post-hoc analyses revealed a significant vmPFC volume × Val66Met interaction ($\chi^2 = 18.03$; $f^2 = 0.36$; $p < 0.001$) and there was a significant three-way vmPFC volume × Val66Met × trial interaction on SCR where participants with smaller vmPFC volume who were also Met allele carriers exhibited greater mean SCR magnitudes across the five trials ($\chi^2 = 18.47$; $f^2 = 0.37$; $p < 0.001$ see Fig. 1b and 1c.) compared to the participants in the other 3 groups. Derivative analyses indicated significantly greater changes in mean SCR slope in respect to the vmPFC × Val66Met interaction ($m^{'}$ $(t) = 0.12$; $SE = 0.05$; $z = 2.33$; $p = 0.020$). Threat condition was not significant in the model and vmPFC did not interact with Val66Met on either EMG or HR magnitude.

3.2. Val66Met by IC on psychophysiological response

Overall model effects were significant for EMG, SCR, and HR repeated measures mixed models (*Wald* $\chi^2 = 125.97$; $p < 0.001$; *Wald* $\chi^2 = 105.26$; $p < 0.001$; and *Wald* $\chi^2 = 41.16$; $p = 0.016$). Post-hoc analyses revealed a significant IC volume × Val66Met interaction ($\chi^2 = 15.71$; $f^2 = 0.35$; $p < 0.001$) and there was a significant three-way IC volume × Val66Met × trial interaction on SCR where participants with smaller IC volume who were also Met allele carriers exhibited greater mean SCR magnitudes across the five trials ($\chi^2 = 6.76$; $f^2 = 0.24$; $p = 0.009$; see Fig. 2b and 2c.) compared to the participants in the other 3 groups. Derivative analyses confirmed that Met allele carrying participants with smaller insula volumes exhibited greater changes in mean SCR slope compared to others in the sample ($m^{'}(t) = 0.17$; $SE = 0.05$; $z = 3.05$; $p = 0.002$). Insula volume did not interact with Val66Met on EMG or HR on either trial of threat condition.

3.3. Val66Met by vACC interactions on psychophysiological response

Significant overall model effects were found for EMG, SCR and HR repeated measures mixed models (*Wald* $\chi^2 = 152.00$; $p < 0.001$ *Wald* $\chi^2 = 121.28$; $p < 0.001$, and *Wald* $\chi^2 = 59.81$; $p < 0.001$). No significant two-way interactions were observed. Two significant three-way vACC × Val66Met × trial interactions on SCR was also observed where participants with smaller vACC volume who were also Met allele carriers exhibited greater mean SCR magnitudes across the five trials ($\chi^2 = 6.24$; $f^2 = 0.03$; $p = 0.013$) and over the three threat conditions ($\chi^2 = 7.56$; $f^2 = 0.04$; $p = 0.023$). However, confirmatory interaction analyses did not indicate that participants with smaller vACC volumes who were met allele carriers exhibited significantly greater changes in mean SCR slope compared to others in the sample ($m^{'}$ $(t) = 0.02$; $SE = 0.05$; $z = 1.68$; $p = 0.929$). Further post hoc analyses indicated that the three-way interaction described above may have been driven by the strong Val66Met relationship on SCR magnitude ($\chi^2 = 14.05$; $f^2 = 0.32$; $p < 0.001$).

3.4. Val66Met by dACC interactions on psychophysiological response

Significant overall model effects were found for EMG, SCR and HR repeated measures mixed models (*Wald* $\chi^2 = 144.59$; $p < 0.001$, *Wald* $\chi^2 = 122.82$; $p < 0.001$; and *Wald* $\chi^2 = 122.82$; $p < 0.001$ respectively). No significant two-way interactions were observed.

Post-hoc analyses revealed a significant three-way dACC × Val66Met × trial interaction on SCR where participants with smaller dACC volume who were also met carriers exhibited greater mean SCR magnitudes across the five trials ($\chi^2 = 8.56$; $f^2 = 0.06$; $p = 0.003$). However, confirmatory interaction analyses did not indicate that participants with smaller dACC volumes who were met allele carriers exhibited significantly greater changes in mean SCR slope compared to others in the sample (m' (t) = 0.02; $SE = 0.05$; $z = 1.68$; $p = 0.929$). Derivative analyses confirmed that participants with smaller dACC volumes who were met allele carriers exhibited significantly greater changes in mean SCR slope compared to others in the sample (m' (t) = 0.12; $SE = 0.04$; $z = 3.29$; $p = 0.001$). No significant Val66Met × dACC interactions were observed on EMG or HR (see Supplementary Table for all trial and threat condition interactions).

4. Discussion

We found that Met allele carriers who had smaller vmPFC, dACC, vACC, and IC volumes all exhibited elevated psychophysiological magnitudes across trials and over threat conditions during a fear-potentiated startle paradigm. However, vmPFC and IC volume, but not dACC nor vACC volume, moderated the relationship between Val66Met and psychophysiological response both across trials and over threat conditions. Our results coincide with previous studies that have shown Met carriers are more sensitive to threatening stimuli compared to their Val homo-zygotic counterparts (Mühlberger et al., 2014; Young et al., 2018b) and that these sensitivities might be exacerbated in individuals with smaller brain areas responsible for threat response (e.g. the vmPFC and IC (Lonsdorf et al., 2015; Soliman et al., 2010). This is the first study that we are aware of that has attempted to ascertain the relationship between Val66Met, cortical morphometry, and psychophysiological response in a clinical veteran sample while controlling for important factors such as PTSD diagnosis.

We have previously shown that Met allele carriers' pattern of responding across trials appeared to suggest a deficit in habituation (Young et al., 2018b). The current findings suggest the Met allele-linked deficit in habituation may have its roots in impairments in both prefrontal areas (e.g. vmPFC) and fear (e.g. IC) circuitry. Previous findings have shown that Met allele carriers exhibit significantly less activation in higher cortical areas such as the vmPFC and the subgenual ACC and greater responding in regions associated with fear and threat assessment (e.g. IC, amygdala, and hippocampus (Lonsdorf et al., 2015; Soliman et al., 2010);). Studies have also shown that individuals with PTSD have smaller vmPFC volume and also exhibit vmPFC neurofunctional hypo-activity (Hayes et al., 2012; Meng et al., 2016). Conversely, individuals with PTSD engage in greater insular recruitment when exposed to unpredictable aversive visual stimuli and when viewing fearful faces (Bruce et al., 2013; Simmons et al., 2013). Therefore, the observed deficits in Met allele carrier habituation may be linked to an overactive IC that is further compromised by a limited capacity for the vmPFC to impose top-down regulation of structures that comprise the threat detection system (e.g. hippocampus, amygdala). This in turn could potentially result in increased threat reactivity to innocuous stimuli or in inappropriate situations and make them more susceptible to trauma – related disorders such as PTSD. Indeed, research has shown that Met allele patients respond poorly to exposure therapy compared to their Val-Val counterparts (Felmingham et al., 2013).

vmPFC and IC volume also moderated Val66Met psychophysiological magnitudes across each of the three threat conditions such that met allele carriers' significantly elevated psychophysiological reactivity across each of the threat conditions. Moreover, neither Val66Met × vmPFC × threat nor Val66Met × IC × threat three – way interactions were significant. Rather, and as shown in Figs. 1c and 2c., Met vmPFC and IC slopes both appear to be nearly flat but significantly more elevated compared to their Val-Val counterparts. This suggests that Met allele carriers were exhibiting consistently elevated arousal across all of the threat conditions, irrespective of their PTSD status. vmPFC activation is associated with the successful suppression of emotional responses to negative emotional stimuli and patients with vmPFC lesions show deficits in emotional responses and emotion regulation (Hänsel and von Känel, 2008). Furthermore, functional imaging studies have also shown a well-established top down inhibitory relationship with the vmPFC on the amygdala. Given that vmPFC is also a subcomponent of the default mode network, our results may suggest a process where Met allele carriers, particularly those with reduced vmPFC volume have an impaired ability to relinquish vigilance to external cues and switch to passive neutral mentation. On the other hand, smaller IC volume is associated with IC overactivation in traumatized individuals (Akiki et al., 2017). Given the importance of the IC to the neurological threat response system, this overactivation along with diminished top-down control exerted by the vmPFC may leave Met allele carriers in a state of continuous basal hyperarousal, which in turn may be associated with difficulties attuning to external safety cues in the environment.

The molecular mechanisms that underlie the observed vmPFC and IC moderated exaggerated psychophysiological response in Met carriers remain speculative but they may lie in an impairment of LTP. Specifically, Met allele carriers may have a reduced capacity to consolidate information regarding non-threatening stimuli due to reduced BDNF-modulated deficits in LTP in the presence of a smaller vmPFC. It is known that the Met genotype is associated with lower peripheral BDNF levels in humans and animal analogues (Ozan et al., 2010). And while it is unclear what relationship peripheral BDNF has to brain function, research has shown that reduced levels of BDNF interfere with basal synaptic transmission and LTP potentiation in limbic (e.g. hippocampus) and but also cortical areas (Cunha et al., 2010). In this way, Met allele carriers' blunted capacity to habituate to the startle probe may stem from reduced synaptic BDNF expression, which in turn interferes with vmPFC activity in general and vmPFC LTP in particular when the vmPFC is reduced in size. This theory is substantiated by rodent research that has shown that Met mice in addition to having smaller vmPFC volume, also exhibit decreased levels of cFos expression along with reduced dendritic complexity in their vmPFC (Yu et al., 2009). Similarly, while substantially less attention has been given to the IC's role in LTP as it relates to Val66Met and threat sensitivity, there is some research that shows that the direct infusion of BDNF into the IC is associated with increased LTP along with dramatically increasing taste aversion extinction efficiency in rats (Escobar et al., 2003; Rodríguez-Serrano et al., 2014). Therefore, it is possible that Met allele-related reduced BDNF expression in insular neuronal synapses might also impair IC LTP and be linked to IC over activation, which would also impair habituation.

Our results may also be linked to hypothalamic-pituitary-adrenal (HPA) axis dysregulation. We have previously shown that Met allele carriers with PTSD in this sample exhibited HPA axis dysregulation as evidenced by increased cortisol suppression during a dexamethasone challenge (Young et al., 2018b). Others have also found similar findings that suggest a relationship between Met allele carriers and HPA axis dysregulation in both non-clinical and clinical populations (Armbruster et al., 2016; Schüle et al., 2006). Furthermore, research suggests that glucocorticoids moderate NMDA receptor expression by increasing the number of NMDA receptors within the synapse during episodes of acute stress, which in turn facilitates LTP via metaplastic processes within the prefrontal cortical areas (Timmermans et al., 2013). However, these processes can be impaired during episodes of saturated binding of glucocorticoid receptors linked to chronic stress by reducing postsynaptic NMDA expression. While more research is needed to confirm this, given BDNF is important for synaptic plasticity and that lower levels of this factor have been linked to LTP interference (Cunha et al., 2010), HPA axis dysregulation may compound BDNF-related vmPFC and IC LTP impairments while also increasing basal arousal levels in Met allele carriers.

We did not find any association between Val66Met SNP on any of the structural volumes of our regions of interest. A previously described study showed reduced activation in the subgenual ACC, which is neuroanatomically adjacent to the vACC in Met allele carriers during fear conditioning (Lonsdorf et al., 2015). We have also previously shown a relationship between ACC size and PTSD on psychophysiological response where individuals with PTSD who had smaller ACC volumes exhibited greater startle magnitudes (Young et al., 2018a). Given that the ACC is bidirectionally innervated by the vmPFC, it may be that the effect of the Val66Met polymorphism on the ACC is influenced by BDNF effects in the vmPFC, IC and possibly other regions. Our divergent findings may also be explained by differences in sampling and analysis as Lonsdorf et al. used functional magnetic resonance imaging paired with fear conditioning in a mostly young university student sample compared to our older, more traumatized, Veteran clinical sample.

Our findings have several clinical implications. First, our research adds neurobiological evidence as to why certain exposure therapies might be less effective for Met allele carriers with PTSD, given their difficulties with threat sensitivity (Felmingham et al., 2013). Given that all of the predominant PTSD psychotherapeutic treatments engage elements of habituation and fear extinction learning (Malejko et al., 2017), less intense exposure therapies (e.g. CBT) may be warranted. Secondly, our findings may indicate that targeted therapies designed to increase synaptic BDNF expression in the vmPFC and IC may hold the potential to reduce symptom severity in Met allele carriers with PTSD and anxiety disorders. For example, research has shown that transcranial magnetic stimulation (TMS) increases BDNF affinity for tyrosine kinase B (TrkB) in prefrontal cortical areas in rats, which may increase synaptic efficiency and promote LTP at a molecular level (Wang et al., 2011). Therefore, TMS that directly targets the vmPFC and IC also may be particularly beneficial in aiding PTSD/anxiety disorder exposure-based psychotherapy uptake in Met allele carriers with intractable threat sensitivity (Philip et al., 2018). Additionally, D – cycloserine, which appears to enhance excitatory neurotransmission (glutamate) mediated by NMDA receptors, has been shown to facilitate the consolidation of fear extinction

potentially by increasing medial PFC BDNF synaptic expression (Andero and Ressler, 2012). Moreover, there is evidence that D – cycloserine is associated with an augmentative effect in some individuals with PTSD undergoing exposure therapy (Mataix-Cols et al., 2017). While more research is needed, D – cycloserine's effects as a psychotherapy adjunct to may be particularly helpful for Met allele carriers with smaller vmPFC/IC volumes diagnosed with PTSD or anxiety disorders and have intractable threat sensitivity by increasing fear extinction consolidation (Myers et al., 2011).

We also must note several limitations. First, our sample was relatively small for a genetic study. Although other recent studies that have published on Val66Met with similar or smaller sample sizes (Frodl et al., 2014; Marusak et al., 2016), other studies with larger sample sizes are needed to assess the reliability of our findings. Our sample also was made up of mostly male white Veterans, which limits generalizability. Thirdly, this study is cross-sectional and therefore we can make no causal inferences from the present findings. Additionally, the lack of functional imaging in the current study only affords us the capacity to speculate how these findings relate to brain function. We also only observed on SCR and (marginally) EMG. This may due to a number of reasons including but not limited to SCR being particularly sensitive to the vmPFC/IC – Val66Met relationship. Other studies will be needed to explore this further.

In conclusion, our results suggest that Met positive individuals may exhibit a deficiency in psychophysiological habituation along with elevated basal arousal levels, whose effects are moderated through reduced vmPFC and IC volumes. Based on the interpretation of our results, the combination of Met allele carrier status and vmPFC and IC volume deficits may confer an increase in susceptibility to anxiety disorders and negative outcomes after trauma exposure (e.g. PTSD) via an increase in threat sensitivity. While more research is needed, our results also suggest the need to see if this subgroup shows a differential course of illness or response to existing treatments. Future neurofunctional imaging studies examining patient cohorts with and without the Val66Met polymorphism that also implement therapeutic interventions hold potential to further elucidate the clinical implications of these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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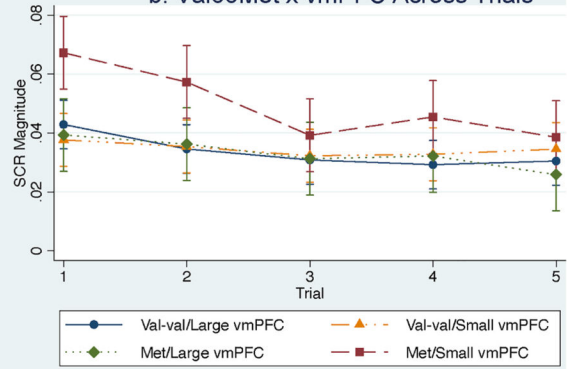
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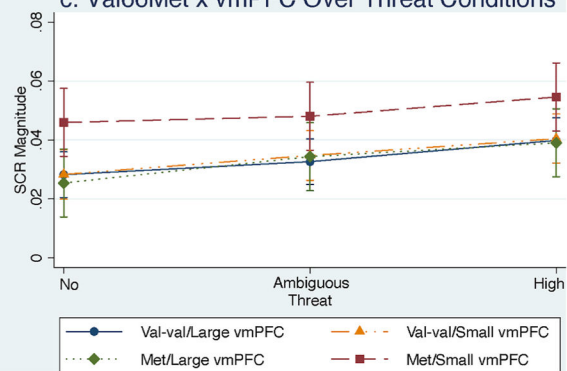
a. Image of the vmPFC (outlined in white)
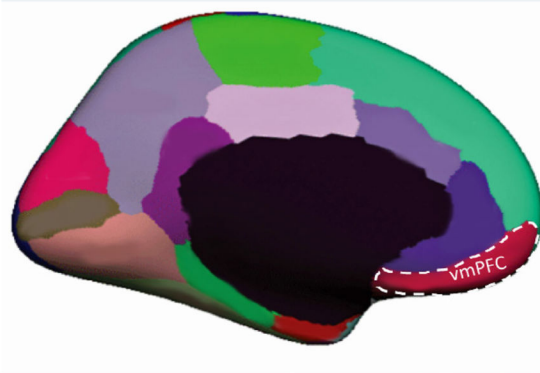
b. Val66Met x vmPFC Across Trials

c. Val66Met x vmPFC Over Threat Conditions

Fig. 1.

Note: vmPFC = Ventromedial Prefrontal Cortex; Figure 1a. Provides a left sagittal plane view of the vmPFC for orientation purposes only and is not representative of lateralization. SCR (y-axis) = skin conductance response and was measured in μS across startle trials (Figure 1b. x-axis) and over threat conditions (Figure 1c. x-axis). The top and bottom vmPFC volume quartiles were dichotomized in Figures 1b and c for visual clarity.
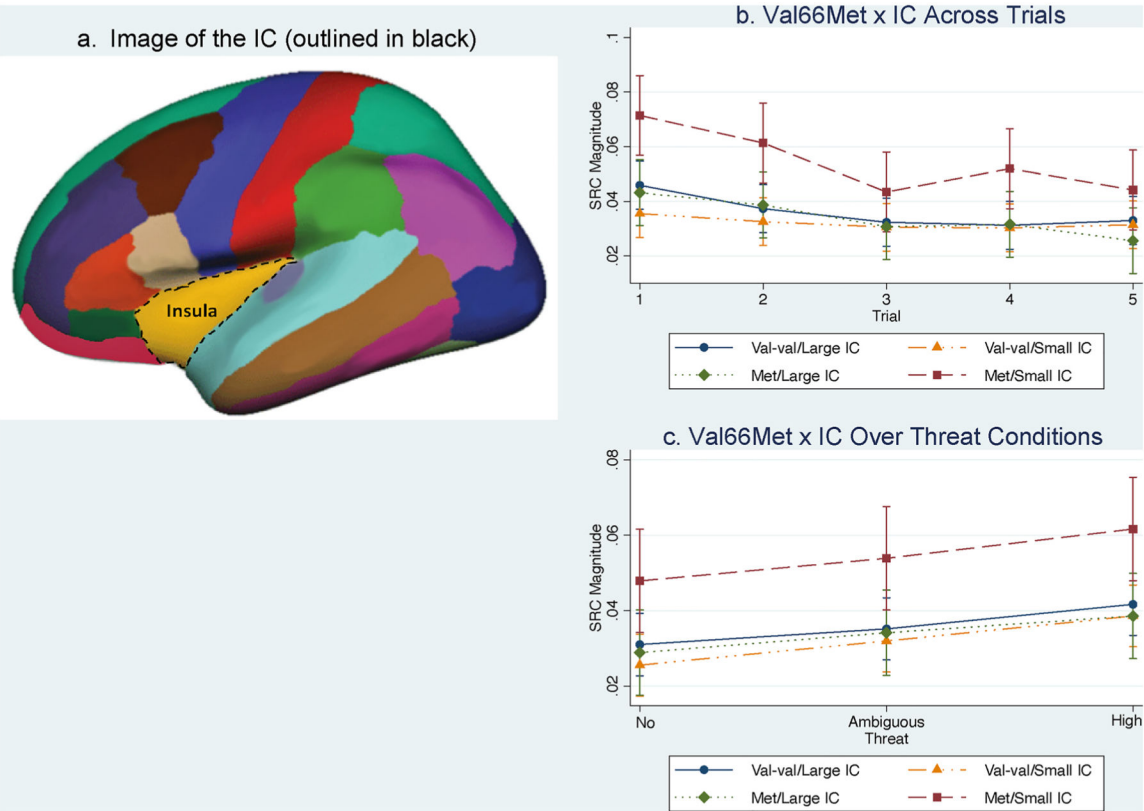
Fig. 2.

Note: IC = Insular Cortex; Figure 2a. Provides a left hemisphere view of the IC for orientation purposes only and is not representative of lateralization. SCR (y-axis) = skin conductance response and was measured in μS across startle trials (Figure 2b. x-axis) and over threat conditions (Figure 2c. x-axis). The top and bottom IC volume quartiles were dichotomized in Figures 2b and c. For visual clarity.

Table 1

Sample descriptive statistics by Val66Met allele (N = 110).

Characteristics		Val-val	Val-met/Met-met	Total
N (%)		73 (66.36)	37 (33.64)	110 (100)
Sex				
	Male	61 (55.46)	32 (29.09)	93 (84.55)
	Female	12 (10.91)	5 (4.55)	17 (15.45)
Race				
	Asian/PI	3 (2.73)	3 (2.73)	5 (5.46)
	Black	16 (14.55)	5 (4.55)	21 (19.09)
	Latino	5 (4.55)	4 (3.64)	9 (8.19)
	White	47 (42.73)	25 (22.73)	72 (65.46)
	Other	0 (0.00)	2 (1.82)	2 (1.82)
Trauma Exposure				
	Adult trauma	42 (38.18)	27 (24.55)	69 (62.73)
	PTSD diagnosis	17 (15.45)	9 (8.19)	26 (23.64)[+]
Gulf War Illness		11 (10.00)	7 (6.36)	18 (16.36)
Alcohol Use Disorder		15 (13.64)	10 (9.09)	25 (22.73)
Mean (SD)				
Age		45.81 (10.02)	45.16 (10.46)	45.49 (10.13)
Education[a]		14.96 (2.04)	15.26 (2.23)	15.06 (2.10)
Intracranial volume[b]		14.27 (0.10)	14.27 (0.10)	14.28 (0.10)
dACC volume[b]		8.25 (0.17)	8.28 (0.19)	8.26 (0.18)
vACC volume[b]		8.30 (0.15)	8.31 (0.19)	8.30 (0.16)
vmPFC volume[b]		10.07 (0.11)	10.09 (0.12)	10.08 (0.11)
IC volume[b]		9.45 (0.11)	9.43 (0.11)	9.45 (0.11)
EMG[c]		2.34 (1.31)	1.68 (1.46)	2.10 (1.46)
SCR[c]		0.05 (0.4)	0.06 (0.05)	0.05 (0.05)
HR[c]		0.12 (0.12)	0.16 (0.14)	0.15 (0.13)

Note: SD = standard deviation; PI = Pacific Islander;

[a] Education is given in years;

[b] volume is given in natural log transformed mm^3;

[c] EMG, SCR, and HR are averaged across trials and threat conditions; N (%) and mean (SD) pairwise statistics were assessed with χ^2 and *t* tests respectfully.

[+] $p < 0.10$.