A Pilot Study: Is the BDNF Val66Met Polymorphism an Important Individual Difference in Understanding Dysregulated Response Monitoring in Generalized Anxiety Disorder?

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INTRODUCTION

Generalized anxiety disorder (GAD) is the most commonly diagnosed anxiety disorder (Wittchen, 2002; Ballenger et al., 2001) with core features that include uncontrollable worry about everyday concerns, heightened anticipation of negative outcomes, and excessive concerns about mistakes (Ladouceur et al., 1998; Dugas et al., 1998; Brown et al., 1993; Kendall et al., 2004; Dugas, Marchand , & Ladouceur, 2005).

GAD is a heterogeneous disorder. It is frequently comorbid with depression and other anxiety disorders (Ballenger et al., 2001) and the spectrum of comorbid disorders is wider for GAD compared to any other anxiety disorder (Kessler, 2000).This heterogeneity poses a challenge to identifying core etiological and treatment mechanisms.

In the current study we focused on two candidate biosignatures for neurocognitive dysfunction in GAD:

1) Error-related brain activity measured via Event-Related Potentials (ERPs)
Response monitoring is the process of noticing and evaluating when a discrepancy exists between our actions and our goals (e.g., an error). GAD has been characterized by enhanced neurophysiological responses to errors evidenced by two error specific ERPs: the Error-Related Negativity (ERN) and Error Positivity (Pe) (Weinberg, Olvet, & Hajcak, 2010; Weinberg, Klein, & Hajcak, 2012; Weinberg, Kotov, & Proudfit, 2014; Xiao et al., 2011).

2) BDNF Val66Met Single Nucleotide Polymorphism
BDNF Val66Met is a human single nucleotide polymorphism (SNP) in which a valine (Val) is substituted by a methionine (Met) at codon 66. The Met allele may be a risk allele for anxiety (Jiang et al., 2005) It has been associated with both increased anxiety-related behaviors in rodent models, and anxious temperament and a higher incidence of mood and anxiety disorders in humans. Those with this risk allele for anxiety may be more likely to show predicted disruptions in error monitoring.

HYPOTHESES

Central ERP Hypothesis
GAD versus a control group will show increased ERN and Pe amplitudes to errors compared to correct trials.

Exploratory Hypothesis
Increased error monitoring measured via event-related brain potentials in GAD would be further enhanced in those with the BDNF Val66Met SNP.

METHOD

Participants
15 participants met criteria for GAD (13 female; M^{AGE} = 22.40, *SD* = 5.33)
- Standard Clinical Interview for DSM Disorders (SCID-I/P; First, Spitzer, Gibbon, & Williams, 2002) interviewed
- 4 met criteria for past MDE
- 7 GAD participants met criteria for additional current Axis I disorders (4 Specific Phobia; 2 Post-Traumatic Stress Disorder; 2 Social Phobia; 2 Dysthymia; 1 Panic Disorder)
- 5 Five GAD participants met criteria for multiple current diagnoses

15 age-matched controls (11 female; M^{AGE} = 22.27, *SD* = 4.82)

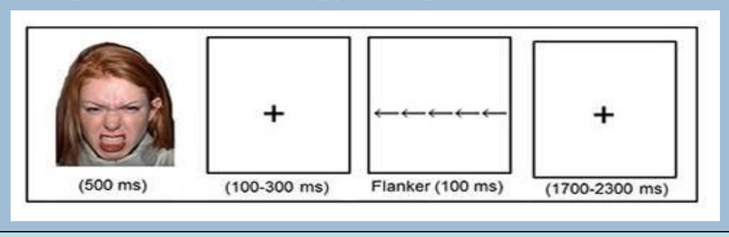
Emotional Faces
Faces of 16 actors portraying angry and neutral expressions were shown for a total of 32 face stimuli (Tottenham et al., 2009). Each face stimulus was shown 45 times.

Modified Flanker Task
A modified flanker task was used for this study. This task requires the participant to identify the direction (right or left) of the central arrow that is flanked by either four arrows facing the same direction (congruent trial) or the opposite direction (incongruent trial). In addition, this study used both facial primes (angry and neutral) and had no face trials.

The task was a total of 3 blocks (no face, neutral face, angry face), with 480 trials per block. In order to avoid carryover effects from the angry condition, the order of experimental blocks was not counterbalanced. Two hundred and forty of the trials in each block displayed congruent flankers while 240 trials displayed incongruent flankers. Eighty practice trials preceded the first block with an 80% accuracy score necessary to begin the experimental blocks.

RTs and accuracy data were recorded. Trials with RTs faster than 200 ms and longer than 800 ms after flanker presentation were excluded from analyses.

Figure 1. Experimental Procedure of an Angry Face Congruent Trial



EEG Recording and Analysis
EEG was recorded continuously via 64 Ag/AgCl scalp electrodes at a sampling rate of 512 Hz. All data were re-referenced offline to an average reference and filtered with a high pass frequency of .1 Hz and a low pass frequency of 30 Hz.

ERP reduction using Brain Vision Analyzer
- Ocular correction was performed (Gratton & Coles,1983).
- ERN was calculated as the mean amplitude between 10-50 ms at FCz.
- Pe was calculated as the mean amplitude between 140-340 ms at Cz.
- Correct response negativity (CRN) and correct error positivity were also evaluated in the same time windows and electrodes respectively.
- Furthermore, to measure the difference in response monitoring on error compared to correct trials, difference scores for error minus correct trials were calculated in both the ERN/CRN and Pe/Pe on correct trials time windows, referred to as the ΔERN and ΔPe respectively.
- Response-locked data were segmented for each trial beginning at 200 ms before each response onset to 1000 ms after stimulus onset.
- The 200 ms window from -200 ms to 0 ms prior to response onset was used for baseline correction.

RESULTS

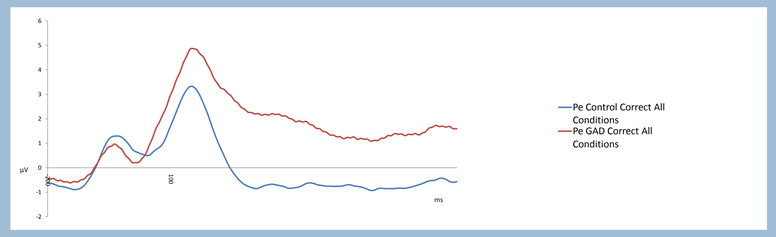
ERP Hypothesis: GAD versus control group will show increased ERN and Pe amplitudes to errors compared to correct trials.

ERN
First, a 3 (Face Condition: no, neutral, angry) x 2 (Correctness: error, correct) x 2 (Group: GAD, control) mixed-design factorial ANOVA was conducted for ERN mean amplitudes. Mean ERN amplitudes did not differ between the GAD and control groups.

Pe
A 3 (Face Condition: no, neutral, angry) x 2 (Correctness: correct, incorrect) x 2 (Group: GAD, control) mixed-design factorial ANOVA was conducted for Pe amplitudes.

There was a significant Correctness x Group interaction, $F(1,28) = 4.34$, $p = .046$, $\eta^2 = .13$. Pairwise comparisons revealed that for correct trials, Pe amplitudes were of greater magnitude in the GAD group (M_{GAD} = 2.90, *SD* = .73) compared to the control group ($M_{CONTROL}$ = .82, *SD* = .73), $p = .054$. However, on error trials, Pe amplitudes did not differ between groups ($p = .72$). In both groups, Pe amplitudes were significantly more positive on errors compared to correct trials (both *p*'s <.03).

Figure 3. Pe amplitudes to correct trials were significantly elevated across all conditions in the GAD versus control group.

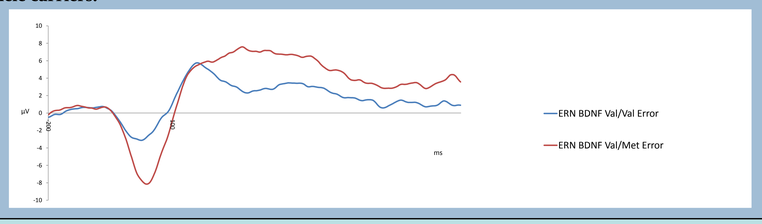


BDNF Genotyping Results
- Overall, 9 of 30 participants had the BDNF Val66Met SNP
- Control group: 3 of 15 participants had the BDNF Val66Met SNP
- GAD group: 6 of 14 participants had the BDNF Val66Met SNP
- Based on these numbers, we decided to explore the BDNF SNP within the GAD group for underlying differences in response monitoring

BDNF Val66Met Hypothesis: Increased error monitoring in GAD would be further enhanced in those with the BDNF Val66Met SNP

ERN
Across all conditions, independent samples t-tests revealed that ERN amplitudes on error trials were significantly more negative in the BDNF Val66Met group (*M* = -6.98, *SD* = 3.82) versus GAD participants without the SNP (*M* = -3.56, *SD* = 1.97), $t(12) = 2.38$, $p < .035$. No significant findings emerged on correct trials.

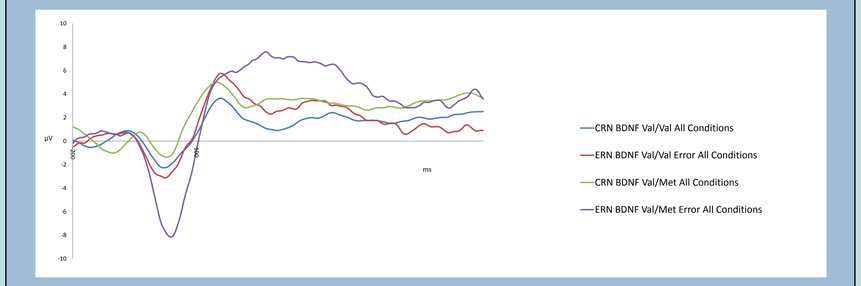
Figure 4. Overall, ERN amplitudes following errors were significantly more negative for BDNF Met allele carriers.



ΔERN

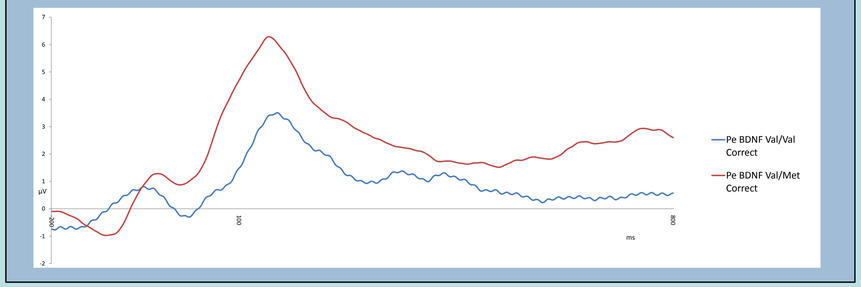
Across all conditions, independent samples t-tests revealed that ERN amplitudes on error minus correct trials were significantly more negative in the BDNF Val66Met group (*M* = -5.68, *SD* = 2.72) versus GAD participants without the SNP (*M* = -1.22, *SD* = 2.28), $t(12) = 3.34$, $p = .041$.

Figure 5. Overall, the difference between ERN amplitudes on error and correct trials was significantly larger for BDNF Met allele carriers.



Pe
Across conditions, independent samples t-tests revealed that Pe amplitudes on correct trials were significantly more positive in the BDNF Val66Met group (*M* = 4.23, *SD* = 2.56) versus GAD participants without the SNP (*M* = 1.45, *SD* = 1.99), $t(12) = -2.30$, $p = .041$. The above result mirrors the group x correctness interaction from the total sample analyses.

Figure 6. Overall, Pe amplitudes following correct trials were significantly more positive for BDNF Met allele carriers.



DISCUSSION

GAD participants showed enhanced Pe after correct response compared to controls suggesting inefficient allocation of response monitoring resources and reduced flexibility (i.e., reduced discrimination between errors and correct trials).

Interestingly, the predicted ERN findings only emerged for the BDNF met allele carriers. Thus, the presence of the Met allele may be an important individual difference reflecting core neurocognitive disruptions associated with clinical anxiety.

These findings further suggest that clinical diagnosis alone may reflect too much phenotypic diversity, thus reducing predictive power in relation to neurocognitive individual differences like error monitoring.

By looking at BDNF genotypes we are exploring an individual difference that may be relevant in disruptions in error monitoring. Combining behavioral symptoms with more biologically informative measures such as genotyping and ERP amplitudes may help to cut across broad dimensions of psychopathology.

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