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## Neural Correlates of Treatment in Adolescents with Generalized Anxiety Disorder: A Preliminary Investigation

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**Authors**

Julie Maslowsky, Karin Mogg, Brendan P. Bradley, Erin B. McClure-Tone, Monique Ernst, Daniel S. Pine, and Christopher S. Monk

Running Head: NEURAL CORRELATES OF TREATMENT

Neural Correlates of Treatment in Adolescents with Generalized Anxiety Disorder: A  
Preliminary Investigation

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Institute of Mental Health and analyzed at University of Michigan.

ABSTRACT

*Objective:* Generalized anxiety disorder (GAD) is a prevalent and debilitating psychiatric condition in adolescence. Two effective forms of treatment are cognitive behavioral therapy (CBT) and selective serotonin reuptake inhibitors. This pilot study examined changes in brain function following each type of treatment in GAD.

*Method:* Subjects were 14 youth with GAD (7 had CBT, 7 received fluoxetine) and 10 age- and gender-matched healthy peers. fMRI scans were acquired before and after treatment for patients, and over two comparable time points for controls. During fMRI acquisition, a probe detection task with emotional (angry, happy) and neutral faces allowed for assessment of neural response to threat. Following previous research, region of interest analyses were performed in the right ventrolateral prefrontal cortex (VLPFC).

*Results:* fMRI results showed increased VLPFC activation, relative to controls, in the medication ( $t(15) = 3.01, p < 0.01$ ) and CBT ( $t(15) = 3.22, p < 0.01$ ) groups following treatment.

*Conclusions:* This study shows significant increase in VLPFC activation in response to angry faces following treatment with CBT or fluoxetine for GAD. This is consistent with previous research indicating that the VLPFC may facilitate effective responding to underlying neural correlates of anxiety in other brain regions, such as the amygdala.

## INTRODUCTION

Generalized Anxiety Disorder (GAD) is a prevalent and debilitating psychiatric condition characterized by excessive worry, hypervigilance, and apprehension about future events (American Psychiatric Association, 2000). Anxiety disorders are associated with impairment in daily life functioning (Ezpeleta et al. 2001) and predict high risk for future problems (Kessler et al. 2008; Pine et al. 1998). Nevertheless, neurological correlates of GAD remain poorly understood. There is a particular dearth of research on changes in brain circuitry associated with improvements in GAD.

In adults, anxiety disorders are associated with increased activation in inferior frontal and medial orbitofrontal cortices in response to anxiety provocation (Rauch et al. 1997). Adolescents with GAD also show altered patterns of neural activation in ventral prefrontal cortex (vPFC). Monk et al. (2006) found GAD patients showed greater ventrolateral (VLPFC) activation than healthy peers when viewing angry faces. Further, VLPFC activation was negatively correlated with their symptom severity, suggesting that VLPFC activation may serve a compensatory function in GAD.

Two known, comparably effective treatments for GAD in children and adolescents are cognitive behavioral therapy (CBT; Butler et al. 2006; Compton et al. 2004) and selective serotonin reuptake inhibitors (SSRIs; Birmaher et al. 2003; Research Unit on Pediatric Psychopharmacology Anxiety Study Group 2001; Walkup et al. 2008). CBT employs techniques such as cognitive restructuring, relaxation, and self-monitoring to ease anxiety symptoms and teach coping strategies (Lang 2004). Recent meta-analyses have consistently shown its effectiveness in reducing anxiety symptoms in adult patient populations (Butler et al. 2006). CBT shows moderate to large effect sizes in comparison to no treatment and nonspecific

psychotherapies (Gould et al. 1997). Meta-analyses also show consistent evidence that the effects of CBT are sustained over at least a 12-month period following successful treatment (DeRubeis & Crits-Christoph 1998).

SSRIs have also been shown to effectively reduce symptoms in pediatric anxiety disorders including GAD (Research Unit on Pediatric Psychopharmacology Anxiety Study Group 2001; Seidel & Walkup 2006; Walkup et al. 2008). Treatment with fluoxetine versus placebo is associated with significantly reduced anxiety symptoms and improved global functioning (Birmaher et al. 2003). Additionally, continued treatment with fluoxetine versus no medication following an initial period of medication treatment is associated with improved outcomes one year later (Clark et al. 2005), indicating potential use in maintenance therapy. Thus, although both CBT and SSRIs have demonstrated comparable efficacy as treatments for GAD, the functional neurological changes that accompany the clinical improvement noted with these treatments are unclear.

The research on the neural effects of psychotherapy on GAD specifically is sparse. However, neuroimaging studies of the effects of psychotherapy in other major psychiatric disorders have shown significant changes in patients' functional activation following treatment (for reviews see Linden 2006; Roffman et al. 2005). Roffman et al. (2005) note that despite wide variations in type and number of diagnoses, type of psychotherapy, and method of neuroimaging, these studies have shown a pattern of consistent attenuation of abnormal activation patterns in regions associated with the pathophysiology of anxiety disorders. No known studies have examined the neural correlates of CBT treatment for GAD. However, at least one study has examined effects of CBT treatment in adult patients with major depressive disorder (MDD). Goldapple et al. (2004) noted decreases in ventral and medial PFC activation while viewing sad

faces following CBT treatment for MDD. As MDD and GAD are known to be highly comorbid (Angold et al. 1999; Kessler et al. 2008), these results further implicate ventral and medial PFC in treatment response for mood and anxiety disorders.

Studies on the neurological effects of SSRI treatment in GAD are similarly lacking. In untreated adolescents with GAD, Monk et al. (2006) found that higher levels of VLPFC activation were associated with fewer anxiety symptoms. As noted earlier, these results suggest that the VLPFC may serve a compensatory function in GAD. The current study sought to examine changes in brain function following the two types of effective treatments for GAD youth. Based on previous findings (Monk et al. 2006), we expected that patients in each treatment condition, relative to healthy peers, would show altered VLPFC activation to angry faces following treatment. Increased activation following treatment could indicate compensatory activation in the VLPFC. Decreased activation could indicate that less VLPFC activation was needed to compensate for anxiety following successful treatment.

## METHODS

### *Subjects*

The sample consisted of 14 adolescents with GAD divided between two groups, those treated with CBT ( $n = 7$ ) and those treated with medication ( $n = 7$ ), plus a comparison group ( $n = 10$ ). Table 1 contains descriptive characteristics of each group. There were no significant differences in the composition of the groups by age, gender, symptom severity or comorbid diagnosis in the two treatment groups. 16 of the 24 subjects (6 from the CBT group, 6 from the medication group, and 4 controls) were also included in a previous study (Monk et al 2006).

*Procedures*

Patients' diagnosis of GAD was determined using the Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version (K-SADS-PL; Kaufman et al. 1997). All patients received their choice of eight weeks of either CBT or medication treatment. CBT treatment consisted of eight weekly sessions lasting 60-90 minutes each and administered by a licensed clinical psychologist. Sessions focused on exposure and skills training, following manualized curricula (Beidel et al. 2000; Kendall & Hedtke 2006). Fluoxetine treatment was administered according to the protocol of the Research Unit on Pediatric Psychopharmacology Anxiety Study Group (2001). An initial dose of 5mg/day was increased every two weeks as recommended by a clinician up to a maximum of 40mg/day. FMRI scans were performed before treatment and within approximately 2 weeks (15 +/- 7 days) of treatment's end. One potential source of difference between the two treatment groups was that patients in the medication group were still receiving medication at the time of the second scan. However, as discussed below, a comparison of the two groups showed no difference in their VLPFC activation. Nonetheless, the groups were analyzed separately due to the qualitatively different nature of the two treatments.

*Anxiety Symptoms*

Anxiety symptoms were measured at Time 1 and Time 2 using the Pediatric Anxiety Rating Scale (PARS; Research Unit on Pediatric Psychopharmacology Anxiety Study Group 2002) by raters trained to achieve acceptable inter-rater reliability (ICC > 0.70). This 50-item checklist shows good test-retest reliability and sensitivity to treatment-related changes in symptoms.



### *Behavioral Task and Analysis*

A probe detection task (Mogg & Bradley 1999) was used to assess neural responses to threat under controlled presentation circumstances and to allow comparison of the fMRI data with Monk et al. (2006). In an event-related design, subjects viewed pairs of faces (angry/neutral, happy/neutral and neutral/neutral) for 500 ms (Figure 1). Subjects responded by pressing a button to an asterisk that was either on the same (congruent) or opposite (incongruent) side as the emotional face. A total of 36 randomized trials for each condition were included. The main analyses in the current study included only data from those trials in which an angry face was present. Trials in which a happy face was present were also analyzed in order to determine the specificity of any effects to angry faces.

Behavioral data were analyzed using paired-samples t-tests in SPSS. Participants had an overall accuracy rate of 75% or greater (mean percentage correct = 94 +/- 6). Reaction time differences of incongruent minus congruent trials provided a measure of attentional bias, such that positive values indicated attentional bias toward the emotional face and negative values indicated attentional bias away from the emotional face.

### *fMRI Procedures and Analysis*

We used a GE 3T scanner to acquire images with 29 contiguous 3.3-mm axial slices parallel to the anterior commissure/posterior commissure line. We used echo-planar, single-shot gradient echo T2\* weighting (TR=2300 msec; TE=23 msec; field of view=240 mm; 64×64 matrix; 3.3×3.75×3.75 mm voxel). High-resolution T1-weighted volumetric scans used a magnetization-prepared gradient echo sequence (MP-RAGE): 180 1.0-mm axial slices; field of

view=256 mm; number of excitations=1; TR=11.4 msec; TE=4.4 msec; matrix=256×256; TI=300 msec; bandwidth 130 Hz/pixel=33 kHz for 256 pixels; in-plane resolution=1 mm<sup>3</sup>.

Functional imaging data were analyzed using AFNI software version 2.56b (Cox 1996; available at <http://afni.nimh.nih.gov/afni>). Participants were excluded if there was motion greater than 3mm in any direction. In order to mitigate movement, all images were registered to one volume in each run. Data were smoothed using a 6-mm full width at half maximum isotropic Gaussian filter. Incorrect trials and trials with reaction time < 200 msec or > 1000 ms were not included in the fMRI analysis.

A random effects fMRI data analysis was conducted using a two-level procedure. At the subject level, data from each subject were analyzed using multiple regression in AFNI's 3dDeconvolve program. For the conditions of interest (angry/neutral congruent and incongruent), vectors were created containing the onset time of each trial for each condition (blank trials were modeled as an implicit baseline). Onset times for trials in which the subject did not respond or responded incorrectly were modeled in a separate vector as a nuisance covariate. Vectors of stimulus timing for each condition were transformed into reference waveforms of response function using a gamma variate (Cohen 1997). Coefficients were thus produced for each condition from each subject.

The primary effect of interest for the fMRI analysis was response to angry faces. Therefore, contrasts were calculated to compare activation during trials in which an angry face was present (both incongruent and congruent trials) relative to baseline (consistent with Monk et al. 2006). Before performing the group level analysis, individual anatomical data sets were converted to Talairach space. The underlying transformation was then applied to that same individual's functional data in order to convert those images as well. The group level analysis

involved conducting a MANOVA analysis using the AFNI module GroupAna on the main contrast of interest, angry versus baseline trials, to evaluate the neurophysiological response. Two separate 2x2 (group x time) ANOVA analyses were performed. The CBT group and medication group were analyzed separately, and each was compared to the control group. The threshold of significance for all analyses was set at  $p < 0.01$ , uncorrected.

## RESULTS

### *Behavioral Results*

Each group's mean reaction times on the behavioral task are presented in Table 2. We did not test a specific hypothesis for the reaction time data, as this study was not designed to evaluate changes in attentional bias because it was underpowered for this particular purpose. Attention bias scores were examined but, unsurprisingly, these showed no significant results. The two treatment groups did not significantly differ in their attentional bias to angry or happy faces at Time 1 or Time 2. The treatment groups' attentional bias scores also did not significantly differ from controls at either time point. Finally, there was no significant change in attentional bias to angry or happy faces from Time 1 to Time 2 in either treatment group.

### *Anxiety Symptoms*

PARS scores did not differ significantly between the two treatment groups at Time 1 ( $t(12) = -.64, p > 0.05$ ) or Time 2 ( $t(12) = 1.14, p > 0.05$ ). Patients in both treatment groups showed significant improvement in anxiety symptoms with treatment: CBT,  $t(6) = 5.91, p < 0.01$ ; medication,  $t(6) = 3.94, p < 0.01$ .

*fMRI Results*

Following previous work (Monk et al. 2006), we focused our fMRI analysis on the response to angry faces. Specifically, we examined changes in brain activation between Time 1 and Time 2. The contrast of angry face trials versus baseline was analyzed separately in each treatment group versus the control group. The medication group, relative to healthy comparisons, showed a significant increase in VLPFC activation following treatment (Figures 2a and 2b). Two clusters of activation were found, one more ventral (located at (31, 41, 0),  $t(15) = 2.85$ ,  $p < 0.01$ ) and one more dorsal (located at (35, 42, 14),  $t(15) = 3.01$ ,  $p < 0.01$ ).

The CBT group, relative to controls, also showed a significant increase from Time 1 to Time 2 in VLPFC activation (Figure 3) to angry faces versus baseline (located at (41, 55, 1),  $t(15) = 3.22$ ,  $p < 0.01$ ). In addition, surprisingly, this group also exhibited bilateral increases in amygdala activation (right amygdala (27, -7, -12),  $t(15) = 2.74$ ,  $p < 0.05$ ; left amygdala (-17, -9, -14),  $t(15) = 2.54$ ,  $p < 0.05$ ). None of the clusters of activation was significantly correlated with reductions in anxiety symptoms in either group.

To examine the specificity of these increases in right VLPFC activation, we examined the change in activation from Time 1 to Time 2 in the contrast of happy faces versus baseline. Even at a relaxed threshold of  $p < 0.05$ , neither treatment condition was associated with increased VLPFC activation. Thus, the increase in right VLPFC activation following treatment for GAD may be specific to viewing angry faces and not a general effect of viewing emotional faces.

## DISCUSSION

Before considering the implications of these findings, it is important to note the many limitations in the work presented here. For example, this study examined a very small number of

subjects, divided into three groups, and patients presenting with GAD also exhibit frequent, comorbid symptoms. Moreover, treatment assignment was based on subject choice, as opposed to random assignment. As a result, these data should be considered as preliminary. Nevertheless, the current data represent the only repeated fMRI study of any pediatric anxiety disorder. Moreover, the data extend a wealth of other research generating a specific hypothesis about the role of the VLPFC in attention and its relationship to pediatric anxiety (Pine, Guyer, & Leibenluft 2009; Monk 2008). As a result, the findings, despite their preliminary nature, point to important avenues for future research.

Consistent with our first hypothesis, the fMRI results showed increased VLPFC activation, relative to controls, in both medication and CBT groups following treatment. The observed increase in VLPFC activation following treatment for GAD is consistent with existing research implicating this region in self-regulation of anxiety. Ochsner et al. (2004) found right ventral PFC activity increased when healthy subjects were asked to voluntarily down-regulate their negative emotions. Similarly, Phan et al. (2005) found right VLPFC activation increased during down-regulation of negative emotions and reported that this activation was positively correlated with intensity of the negative emotion. It is also consistent with Monk et al. (2006), who showed that increased activation in this region was correlated with lower symptom severity in a group of adolescents with GAD, suggesting a potential compensatory mechanism.

Although both are within the PFC, the regions of activation showing treatment-related change appeared to differ between the CBT and medication groups. Nevertheless, a direct comparison of the CBT and medication groups revealed no significant differences in the PFC. Future, larger studies are needed that will allow these two groups to be contrasted with reasonable statistical power. One additional, but not hypothesized, finding was a significant

increase in bilateral amygdala activation in the CBT group following treatment. This result warrants further study given its known importance in anxiety disorders (Monk et al. 2008, McClure et al. 2007, Stein et al. 2002, Thomas et al. 2001).

### *Conclusions*

Successful treatment of GAD with either CBT or fluoxetine in a sample of adolescents was associated with increased activation in the VLPFC. Greater VLPFC activation may thus constitute one mechanism by which these treatments act to decrease anxiety symptoms. To further ascertain the neural correlates of treatment for GAD, future studies should examine the replicability of these results in larger samples. Additional studies are also needed to determine the stability of these effects after treatment has ended.

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Table 1. Sample characteristics

	CBT	Fluoxetine	Control	Statistic
Age	13.4 (1.7)	13.3 (2.5)	14.5 (1.4)	$F(2,21) = 1.09$
Gender				
Male	3	4	4	$\chi^2(2) = .52$
Female	4	3	6	
Comorbid Diagnosis				
Social Phobia	4	2		$\chi^2(1) = 1.17$
Separation Anxiety	5	5		$\chi^2(1) = 0$
ADHD	2	2		$\chi^2(1) = 0$
MDD	3	5		$\chi^2(1) = 1.17$
Anxiety Symptoms				
PARS, pre treatment	15.4 (3.2)	16.4 (2.5)		$t(12) = -.64$
PARS, post treatment	9.0 (4.8)	5.3 (7.2)		$t(12) = 1.14$

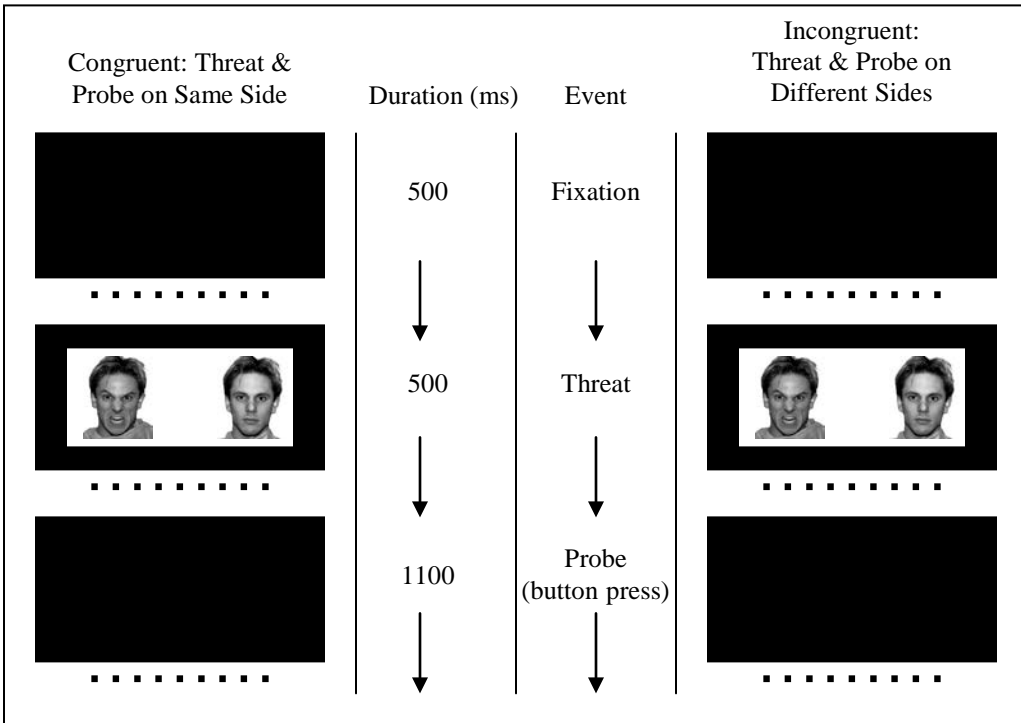
Subject groups did not differ on age or gender, and treatment groups did not differ on comorbid diagnoses or on anxiety symptom scores before or after treatment. CBT, cognitive behavioral therapy. PARS, pediatric anxiety rating scale.

Table 2. Mean reaction times (in ms) on behavioral task by subject group at Time 1 and Time 2

	CBT		Fluoxetine		Control	
	Time 1	Time 2	Time 1	Time 2	Time 1	Time 2
Angry Congruent	543.93	528.23	556.44	483.69	530.13	512.57
Angry Incongruent	549.38	523.51	537.32	499.85	531.91	518.66
Angry Bias (incongruent - congruent)	5.45	-4.73	-19.12	16.16	1.78	6.10
Happy Congruent	553.44	524.30	545.39	498.16	522.83	508.81
Happy Incongruent	552.79	521.73	537.19	498.52	533.86	513.92
Happy Bias (incongruent - congruent)	0.65	2.57	8.21	-0.36	-11.03	-5.12

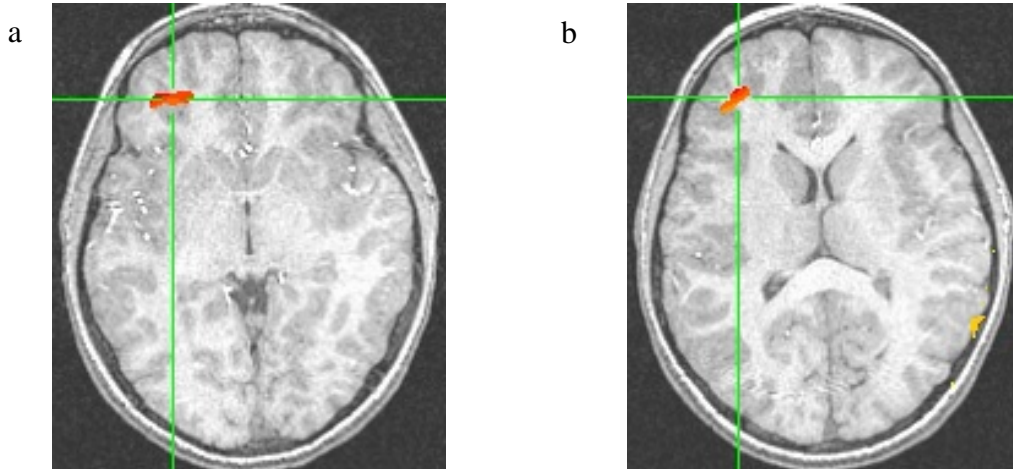
There were no significant differences in reaction time or attentional bias in any condition, either between groups at each time point or within each group from Time 1 to Time 2. Reaction times to happy faces are presented for reference.

Figure 1. Visual Task



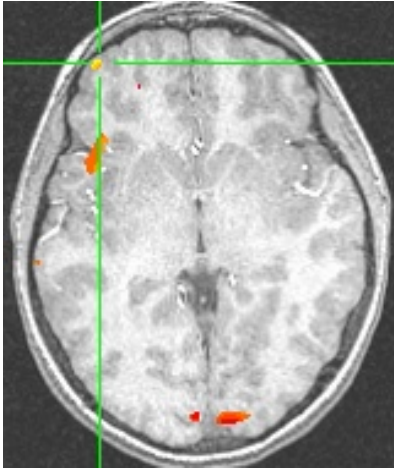
An initial fixation of 500ms was followed by pairs of emotional and neutral faces (angry/neutral and happy/neutral) for 500ms. Subjects then responded by pressing a button to indicate the position of an asterisk that was either on the same (congruent) or opposite (incongruent) side as the emotional face.

Figure 2. Increased VLPFC activation in patients treated with fluoxetine versus controls, Time 2 > Time 1.



Two clusters of activation were noted: a) Right VLPFC (31, 41, 0),  $t(15) = 2.85$ ,  $p < 0.01$ , and b) Right VLPFC (35, 42, 14),  $t(15) = 3.01$ ,  $p < 0.01$ .

Figure 3. Increased VLPFC activation in patients treated with CBT versus controls, Time 2 > Time 1.



Increased activity from Time 1 to Time 2 in Right VLPFC (41, 55, 1),  $t(15) = 3.22$ ,  $p < 0.01$ .



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Figure 1. Visual Task

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