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TITLE: Task-Related Connectivity, Amygdala Volume, and Attentional Control in Anxious Adolescents

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ABSTRACT

Task-Related Connectivity, Amygdala Volume, and Attentional Control in Anxious Adolescents

Anxiety is an incapacitating disorder affecting millions of people that emerges early in life. Past research has focused primarily on behavioral and neurophysiological differences in children and adults and has only recently begun to utilize imaging techniques to study the anxious brain. Much of this literature has focused on the role of the amygdala. However, relatively little is known about the behavior of neural correlates of anxiety during adolescence. This study explored the relationships among task-related functional connectivity, amygdala volume, and negative bias in attention in a community sample of adolescents whose symptoms of anxiety had been measured longitudinally. We found correlations between right amygdala volume and negative bias, and different amygdala-frontal networks showed more or less functional connectivity in more anxious participants. We conclude that some networks are inhibited in anxious adolescents while others are compensatory, and negative bias may be a precursor to more notable symptoms of anxiety.

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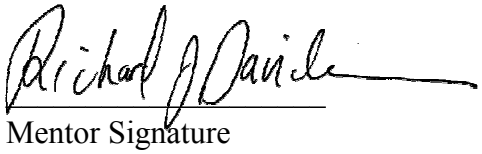

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Senior Honors Thesis

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Introduction

Invisible to the average bystander, anxiety is a debilitating disorder affecting millions of people across the globe. With a median age-of-onset of 11 years old and 28.8% prevalence among Americans (Kessler et al., 2005), anxiety is a common issue for adolescents, adding a layer of complexity to an already trying time of life. After decades of behavioral studies, findings have recently begun to emerge detailing the physical and functional differences of the anxious brain (Kim & Whalen, 2009; Burghy et al., 2012; Fox & Pine, 2012). However, there remains a relative dearth of functional imaging studies designed specifically to look at how individuals develop anxious symptoms and how those symptoms relate to other abilities such as emotion regulation, executive function, and cognitive and attentional control.

Within the behavioral world, several cardinal traits related to routine affective function have surfaced. Among these, an extended negative emotional state relative to non-anxious peers appears quite prevalent; exposure to a negative stimulus engenders negative affect within the anxious person that persists longer than in healthy controls (Newman & Llera, 2011). Further, their response may be more negative to begin with, and they may have difficulty changing their emotional response. Carthy and colleagues (2010) found that, compared to healthy peers, anxious adolescents reported greater negative affect upon viewing a negative scene and demonstrated poorer reappraisal ability when instructed to process the scene in a more positive manner. Mood induction via music has also been found to impact individuals with generalized anxiety disorder (GAD) more than it impacts healthy controls. Participants in a study by Mennin and colleagues (2005) who self-reported GAD with the Beck Anxiety Inventory (BAI) had more intense moods and more negative but not positive moods upon listening to different pieces of

music. They also had difficulty believing that they would be able to calm themselves down and return to baseline after negative mood induction, which was precisely the case.

Anxious individuals also have trouble moving their attention elsewhere when exposed to information that is emotion-laden but irrelevant to the task at hand (Mogg et al., 2000). These individuals' excessive focus on threat-related stimuli demonstrates anxiety's impact on inhibition and shifting, two major aspects of attentional control (Eysenck et al., 2007). Some variation on an affective Stroop test is most commonly used to test this ability, and individuals with more anxious symptoms consistently perform more poorly than their non-anxious counterparts, with slower response times and decreased accuracy (Krug & Carter, 2012). Specifically, higher-anxiety participants experience more Stroop interference from negative stimuli (Blanchette & Richards, 2012). Additionally, more anxiety symptoms are associated with self-reported reduced ability to focus attention on the Attentional Control Scale (ACS; Reinholdt-Dunne et al., 2012). All of these behaviors may be part of a hyper-responsive threat-detection process that characterizes the disorder (Bar-Haim et al., 2007; Bradley et al., 1995; Mathews & McLeod, 2005; Newman & Llera, 2011; Waters et al., 2008). In cases where performance on tasks like the affective Stroop do not vary between anxious and non-anxious participants (e.g., Eysenck, 2007), it is theorized that the anxious participants utilize compensatory strategies; however, this has not been seen in studies using functional magnetic resonance imaging (fMRI).

Numerous physiological studies have also highlighted appreciable differences between those with and without anxiety. Measuring event-related potentials (ERPs) during a go/no-go task, Righi and colleagues (2009) found that despite an equivalent performance to their healthy peers, higher-anxiety participants showed a hyperactivation of the anterior cingulate cortex (ACC) on "no-go" runs, suggesting that the brain compensates for what would otherwise be a

struggle. This demonstrates that even without an emotionally-valenced stimulus, anxious individuals must use different mechanisms to perform such a task. Looking at the other side, Smith and colleagues (2004) studied the startle response and corrugator electromyography in anxious versus healthy subjects upon exposure to images from the International Affective Picture System (IAPS; Lang et al., 2008). Here, more anxious participants showed both increased startle potentiation and corrugator activity when viewing unpleasant images, suggesting a stronger and more negative emotional response. It would appear that anxiety corresponds to both differing brain activity in general, and these individuals' responses—both neurological and physiological—can be seen even more distinctively when in an affective state.

New innovations in neuroimaging, specifically fMRI data, have provided more insight as to how anxious brains process and regulate negative affect, and much of this work has pointed to the crucial role of the amygdala and prefrontal brain regions with which it shares functional connectivity. For example, when shown emotional faces, anxious individuals will have greater amygdala activation in response to fearful faces (Beesdo et al., 2009; Clauss et al., 2010), and higher-anxiety subjects also show stronger amygdala activity when exposed to negative words (Laeger et al., 2012). Interestingly, Laeger and colleagues' study found that these individuals also showed more functional connectivity of the amygdala and dorsolateral prefrontal cortex (dlPFC) whereas most studies have shown that a relative *lack* of connectivity between the amygdala regions and frontal regions like the dlPFC, ventral prefrontal cortex (vPFC), and dorsal ACC (dACC) is associated with anxiety (Basten et al., 2011; Sehlmeyer et al., 2010; Hare et al., 2008; Clauss et al., 2010; Casey et al., 2010). Functional connectivity of the amygdala and insula, however, is generally found to be positively correlated with anxiety symptoms during

resting state conditions (Roy et al., 2013; Baur et al., 2013), though there is debate over whether this is the case during emotional tasks (Jasinska et al., 2012; Simmons et al., 2006).

Amygdala aside, Krug and Carter (2012) also found that in a high-expectancy emotional Stroop task, higher anxiety was correlated with reduced activity in the ventrolateral PFC (vlPFC), anterior insula, and orbitofrontal cortex (OFC). Despite their inconsistencies, all of these previous studies provide insight to the anxious adult brain. However, the adult brain in any condition varies from that of an adolescent, and more investigations must be done regarding adolescent anxiety.

Even in healthy individuals, the adolescent brain shows significant functional differences compared to adults. When faced with a negative stimulus, adolescents show greater amygdala activation than adults or younger children (Casey et al., 2011; Hare et al., 2008), and they also show less prefrontal activity with respect to that amount of amygdala activity (Hare et al., 2008). When researchers compared anxious teens to their non-anxious peers as they performed an affective go-no task in the scanner, this effect was exacerbated, and the individuals with higher trait anxiety also showed consistent amygdala hyperactivation over time as opposed to becoming habituated to the stimulus (Hare et al., 2008). One recent pilot study (N = 20) by Strawn and colleagues (2012) compared functional connectivity between anxious and non-anxious teens; however, when amygdalae were used as the seed regions, the only differences that emerged were in the posterior regions of the brain.

Structural differences in the amygdalae of anxious individuals have also been implicated using neuroimaging techniques, though results are varied. De Bellis and colleagues (2000) found that adolescents with diagnosed GAD have larger right amygdalae than healthy controls, while Milham and colleagues (2005) found that adolescents with anxiety disorders have smaller left

amygdalae than healthy controls. In a study of monozygotic twin pairs, no within-pair differences in amygdala volume emerged when the pair was discordant for anxiety or depression, though the same study found that concordant twins had smaller right amygdalae than healthy control pairs (Alemany et al., 2013). Koolscijn and colleagues (2012) saw no significant associations at all between amygdala volume and internalizing behavior in adolescents.

The first goal of the current study is to determine whether the past studies, many of which involve facial processing, can be generalized to broader situations during adolescence and whether cognitive and neurological results can be predicted by earlier measures of anxiety. We also hope to draw clearer connections between brain connectivity and cognitive function. The proposed study will be a secondary analysis of a large data set examining how symptoms of anxiety during childhood and adolescence predict adolescents' affect-based attentional control and brain activity. The former will be evaluated based on subjects' performance on an affective go/no-go (AGN) task from Cambridge Neuropsychological Test Battery (CANTAB; Cambridge Cognition, 1994), and we hypothesize that more anxious individuals will demonstrate more negative errors of commission, i.e., categorizing a non-negative stimulus as negative, compared to neutral errors of commission due to a lack of cognitive control when exposed to the negative stimuli. Study of brain activity will utilize fMRI task data during which participants viewed unpleasant and neutral IAPS images. In order to examine how anxious individuals process and regulate negative emotion, we will contrast amygdala activity during negative and neutral picture trials. Additionally, we will use both amygdalae as regions of interest (ROIs) in functional connectivity analyses to explore their relations with the frontal regions of the brain with the hypothesis that we will see a relative lack of connectivity between amygdalae and the dlPFC, vlPFC, and ACC in anxious participants. The final goal of this study is to provide further insight

as to the relationship between amygdala volume and anxiety in adolescents, as different studies have found varying results as to whether higher anxiety is correlated with larger or smaller amygdalae. Anxiety symptoms will be assessed using longitudinal self-report data and reports from parents and teachers.

Methods

Participants

Participants were 154 adolescents (82 female, M_{age} = 18.6 years) selected from the Wisconsin Study of Families and Work (WSFW; Hyde et al., 1995). Pregnant women in their second trimester were recruited for the study from clinics and hospitals around Wisconsin in 1990. Women had to be at least 18 years old and living with their husband or partner. 140 participants had usable MRI data. All participants provided informed consent and were compensated $100 for the day. University of Wisconsin-Madison Institutional Review Boards approved all procedures.

Materials and Procedures

Health and Behavior Questionnaire

The MacArthur Health and Behavior Questionnaire (HBQ; Essex et al., 2002) is a measure of mental, physical, and social well-being that was administered to the participants and their primary caregivers routinely throughout the participants' lives. Teachers also provided input during elementary and middle school assessments. The present study utilized an average of participants' HBQ anxiety scores from grade 1 to grade 12 to measure longitudinal symptoms as well as pre-high school scores (ages 7 to 14) and during-high school scores (ages 14 to 18) to determine whether any effects were solely pre- or post-pubescent.

Beck Anxiety Inventory (BAI)

About one month before the fMRI scan day, participants completed questionnaires concerning their mental state, including the Beck Anxiety Inventory (BAI), a 21-question multiple-choice self-assessment of the individual's anxiety over the past week. Each question describes subject-, somatic-, or panic-related symptoms of anxiety and is answered with a scale from 0 (Not at All) to 3 (Severely).

Affective Go/No-Go Task

After the scan, participants performed an affective go/no-go (AGN) task from the CANTAB. Participants saw positive, negative and neutral words presented throughout 20 blocks of the task. Within each block, words from one of the three categories were named the "target," and words from one of the two remaining categories were named the "distractor." Participants were instructed to press a button as quickly as possible upon seeing a word from the block's target category. White words appeared in capital letters one at a time for 500 ms with an inter-stimulus interval of 1000 ms, and there were 18 words per block. The present study focused on participants' negative commissions; i.e., when the target for a block was negative but the participant mistakenly pressed the button upon seeing a positive or neutral word.

Brain Imaging Task

To prepare participants for the MRI scan, each underwent a mock scan in which he or she was positioned in an inactive scanner shell with a head coil and goggles and exposed to sounds that simulated actual scanner noise. Participants also completed a practice version of the

behavioral task, presented with E-Prime (Psychology Software Tools, Pittsburgh, PA) that they would perform in the real scanner.

To obtain structural data, participants entered the scanner and were instructed to rest silently with their eyes closed while remaining "clear, calm, and awake." Following the structural scan, participants completed an implicit emotion regulation task, a modified version of a task previously used in our laboratory (Jackson et al., 2000). Subjects viewed 60 positive (*M* = 7.23/10), 60 negative (*M* = 2.79/10), and 60 neutral (*M* = 4.99/10) pictures from the IAPS (Lang, Bradley, and Cuthbert, 2008). Images were presented using E-Prime for four seconds each at 800 x 600 pixel resolution. Each image was followed by the presentation of a white fixation cross for an average of 10 seconds (range 6.5-18.6 s). The task was broken into five separate runs with 36 trials each. Participants were instructed to keep their eyes on the image or fixation cross throughout each run and to try to not look away even if they found an image to be disturbing.

Imaging Parameters and Data Reduction

Structural and functional images were collected on a 3 T MRI scanner (Discovery MR750, General Electric Medical Systems) with an 8-channel radio-frequency (RF) head coil array. T1-weighted structural images (1 mm^3 voxels) were acquired axially with an isotropic MPRAGE sequence (echo time (TE) = 3.18 ms, repetition time (TR) = 8.13 ms, tip angle (TI) = 450, flip angle = 12 degrees). Participants performed the E-Prime task during collection of five T2*-weighted gradient-echo echo-planar pulse sequences lasting 530 s (265 volumes) each with a TE, TR and flip angle of 25 ms, 2,000 ms and 60 degrees, respectively. Image volumes had a resolution of 3.5 mm × 3.5 mm × 5 mm (matrix size = 64 × 64; 30 sagittal slices).

Amygdalae were segmented using Automatic Hippocampal Estimation using Atlas-based delineation (AHEAD), which has been adapted for the amygdala. (See Hanson et al., 2012 for details.)

fMRI Data Analyses

Pre-Processing: Anatomical data were transformed to Montreal Neurological Institute (MNI) space using an affine transformation computed in AFNI (Cox, 1996) and then segmented with SPM8 (Wellcome Department of Cognitive Neurology, UCL). Diffeomorphic warps to group space were created using DARTEL in SPM8. Each subject's anatomical image was then transformed into group space with the corresponding DARTEL warp. All of these were averaged to make a group-average template, which was then normalized to MNI space to make a transformation matrix with which the individual contrasts were transformed to MNI space. When analyzed, all amygdala volume measures were controlled for total gray matter.

Functional data were slice-time corrected, motion corrected and time-points with motion greater than 2mm were censored out.

Psychophysiological Interaction (PPI) Analysis: The major analyses in the present study were based on a psychophysiological interaction (PPI) model that examined co-activation among regions of the brain, here referred to as functional connectivity, during exposure to negative versus neutral images in the fMRI scanner (Banks et al., 2007). In this model, both the left and right amygdalae were selected as seed regions of interest (ROI) and masks were created of each using the WFU Pick Atlas (Maldjian et al., 2003), which were then warped to individual native space using an inverse transformation matrix from DARTEL. Higher estimates of

functional connectivity in the given conditions are believed to represent increased flow of information between the two indicated areas of the brain.

A generalized linear model (GLM) was estimated with three regressors: a physiological regressor for the amygdala, a psychological regressor representing the task conditions (e.g., negative or neutral images), and a PPI regressor that represented the interaction between the physiological regressor and negative versus neutral image presentation. Participant-specific voxel-wise regression coefficients (β values) of the PPI regressor were warped to MNI space using the transformation matrix from DARTEL and smoothed with a 6mm full-width half maximum Gaussian kernel. Participant-specific β values were entered into a group-level regression with average anxious symptoms throughout childhood and adolescence as a predictor using AFNI's 3dRegAna (Cox, 1996).

Results

In order to examine relationships between attentional control and anxiety, a series of two-tailed Pearson-*r* correlations were conducted. As predicted, longitudinal anxiety was positively correlated with errors of positive ($r = 0.198$, $p = 0.034$), neutral ($r = 0.281$, $p = 0.002$), and negative ($r = 0.273$, $p = 0.003$) commission on the AGN task. However, the difference between negative and neutral commissions was not significantly correlated with longitudinal anxiety ($r = -0.038$, $p = 0.685$). Concurrent anxiety as determined by BAI scores was positively correlated with neutral ($r = 0.220$, $p = 0.016$) and negative ($r = 0.280$, $p = 0.002$) commissions but only correlated with positive commissions at trend level ($r = 0.168$, $p = 0.068$). Again, the difference between negative and neutral commissions was not significantly correlated with BAI-measured concurrent anxiety ($r = 0.070$, $p = 0.447$).

Amygdala volume

Associations between amygdala volume, attentional control, and anxiety were indexed using a series of two-tailed linear regressions. When controlling for total gray matter and gender, right amygdala volume was positively correlated with the negative-neutral contrast ($\beta = 0.336$, $p = 0.005$), while left amygdala volume was correlated to the negative-neutral contrast at trend level ($\beta = 0.221$, $p = 0.073$). No gender effects were detected in either model. Because similar trends were seen bilaterally and no significant difference was observed between them, a subsequent regression was computed using average amygdala volume. As expected, average amygdala volume was significantly positively correlated with negative-neutral commissions ($\beta = 0.292$, $p = 0.018$; see figure 1). Again, no significant gender effects were detected. Focusing on the relations between amygdala volume and anxiety measures, the only significant association that emerged was an inverse association between right amygdala volume and longitudinal anxiety between the ages of 7 and 14 ($\beta = -0.297$, $p = 0.029$; see figure 2).

Functional Connectivity

In the PPI model, voxel-wise inter-regional co-activation between the amygdala and the rest of the brain was estimated as a function of task. Although no associations detected survived multiple comparison correction, several associations of potential interest were identified. Specifically, as predicted, lower estimates of left amygdala to right inferior frontal gyrus (IFG) connectivity were associated with higher overanxious scores as measured by the MacArthur Health and Behavior Questionnaire (Essex et al., 2002) at age 18 ($t = -2.021$, $p = 0.043$). Less left amygdala to left insula functional connectivity was also correlated with more negative relative to neutral commissions on the AGN task ($t = -3.227$, $p = 0.002$), and less left amygdala

and left IFG coupling was predicted by higher in BAI score (t = -2.249, p = 0.026). Further, as BAI score increased across participants, an inverse association in left amygdala-left lPFC functional connectivity was also observed (t = -2.733 p = 0.007). Finally, longitudinal anxiety symptoms also predicted right amygdala-left dlPFC connectivity, though not in the anticipated direction (t = 3.232, p = 0.002). Again, no gender effects were observed in these analyses.

Discussion

The purpose of the current study was to interrogate individual differences in how attentional control and persistent symptoms of anxiety relate to structural and functional differences in the brain in adolescence. As predicted, longitudinal anxiety was positively correlated with errors of all types of commissions in the Affective Go/No-Go (AGN) task; however, when examining the relations between anxiety and our expected negative bias as measured by the difference between negative and neutral commissions, no significant results emerged. Both average and right amygdala volumes, on the other hand, were positively correlated with this negative-neutral contrast when controlling for gray matter. In addition, longitudinal anxiety before high school was also negatively correlated with right amygdala volumes.

Though no associations survived multiple comparison correction, some results from our PPI analyses may be of interest for future studies. As hypothesized, functional connectivity between the left amygdala and left and right IFG as well as left lateral PFC was negatively correlated with measures of concurrent anxiety, and functional connectivity between the left amygdala and left insula was negatively correlated with a negative bias on the AGN, our measure of attentional control. Surprisingly, increased longitudinal anxiety from ages 7 to 18

significantly predicted higher, rather than lower, left amygdala-left dlPFC functional connectivity.

Though we found no relationship between negative bias on the AGN and anxiety, either longitudinal or concurrent, negative bias (negative relative to neutral commissions) was positively correlated with average amygdala volume, suggesting that larger amygdala volumes correspond to poorer performance on cognitive control tasks when these individuals are exposed to negative stimuli. Previous studies have linked these two variables via anxiety; De Bellis and colleagues (2000) found that adolescents with generalized anxiety disorder have significantly larger right amygdalae than their healthy peers, and numerous studies have demonstrated poor attentional control in the presence of negative stimuli in anxious individuals (Mogg et al., 2000; Eysenck et al., 2007; Blanchette & Richards, 2012). Based on these findings, we had initially hypothesized that our measure of attentional control would be correlated with participants' subclinical levels of anxiety, but we did not find any relation of significance between the two variables. However, our significant correlation between right amygdala volume and negative bias in attention may be a subtle hint as to how anxiety arises. For example, negative bias in attention may be more prevalent than other behavioral symptoms of anxiety in subclinical populations, acting as a precursor to or risk factor for diagnosable anxiety later on. Future work in this area could explore different aspects of cognitive control in anxious patients in order to determine whether these processes to indeed rely on similar circuitry.

The results of this study provide some insight into the relations between amygdala volume and adolescent anxiety and offer a basis for future research using functional MRI in anxious adolescents. In particular, we found that when controlling for total gray matter, individuals with more anxious symptoms from ages 7 to 14 had smaller right amygdala volumes

at age 18. However, the same correlation was not seen when including anxious symptoms from ages 14 to 18. This suggests that more so than adolescent anxiety, childhood anxiety may impact brain development, specifically development of the amygdala, which has not yet reached full maturity by that time (Uematsu et al., 2012). It may therefore be more plastic and sensitive to environmental influences.

Although no functional connectivity analyses survived multiple comparison correction, several associations of note were detected and may provide insight as to where future studies might focus. As predicted, concurrent anxiety was negatively correlated with left amygdala-left IFG connectivity, left amygdala-right IFG connectivity, and left amygdala-left lateral PFC in negative relative to neutral image trials. These findings support our hypothesis as well as previous findings such as those from Basten et al. (2011) and imply that these affect-relevant neural pathways may be impaired in those with anxiety. Whereas in healthy controls, these cortical regions may show initial increases in activity representing attempts to regulate or dampen amygdala responses, people with anxiety struggle with this regulation. Furthermore, previous studies also have noted that, following the presentation of emotional stimuli, prefrontal regions will show increased activation followed by decreased amygdala activity in healthy controls (Hariri et al., 2003; Phan et al., 2005; Urry et al., 2006). Thus, emotion regulation therefore seems to involve a down-regulation of the limbic system via prefrontal regions involved in cognitive control. Examining only the first 8 seconds following stimulus presentation, we were not looking to detect this down-regulation, but future studies should consider including a longer timecourse with the hypothesis that the entire network will be malfunctioning in individuals with more anxious symptoms.

When looking at associations with longitudinal anxiety from age 7 to age 18, to our surprise we detected a positive association with functional connectivity between the right amygdala and left dlPFC. Although this contrasts our hypotheses, this association is similar to data from a study by Laeger and colleagues (2012) who found increased functional connectivity between these the left amygdala and left dlPFC in anxious individuals when they were shown negative words. Given this inconsistency in the literature, we believe that our data represent potential hyperactivity in individuals with subclinical anxiety. Following the right amygdala's response to a negative image, the left dlPFC may quickly activate in order to compensate for the diminished responses by other frontal regions and the insula that we observed. As this relationship only emerged when examining longitudinal anxiety, it may be that this pathway strengthens as a response to other inhibited pathways over time. Such a compensatory mechanism would help explain the lack of relationship that had been expected between anxiety and attentional control in our study.

Although the present study yields some surprising as well as promising associations, there are some limitations of note. First, although longitudinal behavioral data were available, the present study was limited in that participants were only scanned at one time point in adolescence. Thus, we were unable to parse apart potential associations between cognitive control, anxiety, and amygdala development and connectivity over time. Second, the selected affect regulation imaging task was relatively passive, and attentional control was assessed outside of the scanner. Future work could benefit from tasks which combine both regulation and cognitive demands in more direct ways. For example, much of the previous data has been compiled using the Affective Stroop task (e.g., Krug & Carter, 2012; Eysenck et al., 2007), which would be a good candidate here. Finally, as previously mentioned, participants in this

study came from a community sample and were not selected for anxious symptoms and tended to score low on anxiety measures. Future work could benefit from using clinically anxious samples. Future studies in the area should expand the fMRI measurements and work to scan children and adolescents at the same time points when behavioral data is collected. Experimenters could then compare trajectories of different functional connectivity across the lifespan and begin to determine the causality within relationships between neuroimaging data and behavioral and cognitive data. Ideally, measures of attentional control would also be taken with the participant in the scanner. Studies could also compare healthy controls to children and adolescents with diagnosed generalized anxiety disorder or attempt to recruit a subclinical population with more variance in anxious symptoms.

Anxiety in adolescence is a field that remains ripe for future research. The teen years are a time of rapid neurological and behavioral changes for all individuals, and adding symptoms of anxiety into the mix makes it an even more trying period in life. Our results suggest that by age 18, both structural and functional differences in the brain can be seen among individuals with more or less anxious behavior and levels of attentional control. Future studies should further investigate these differences in hopes of gaining a better understanding of adolescent anxiety and insights into how it may be most effectively treated.

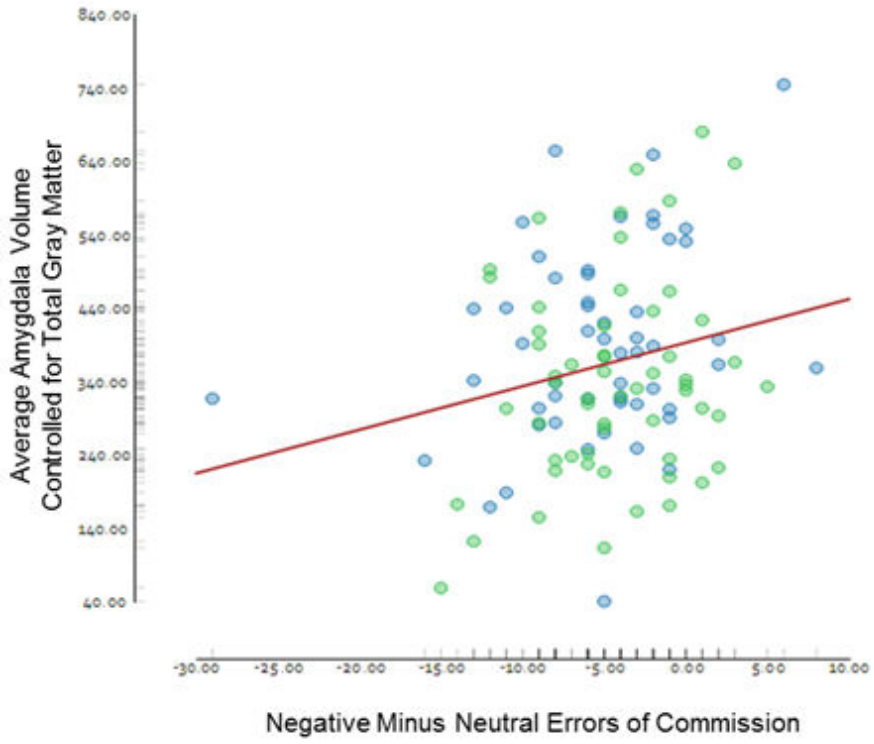

Figure 1: Negative bias in attention as measured by the difference between negative and neutral errors of commission on the CANTAB Affective Go/No-Go task (Cambridge Cognition, 1994) is significantly correlated with average amygdala volume when controlling for total gray matter ($p = 0.018$). Males are represented with blue dots, females with green dots.

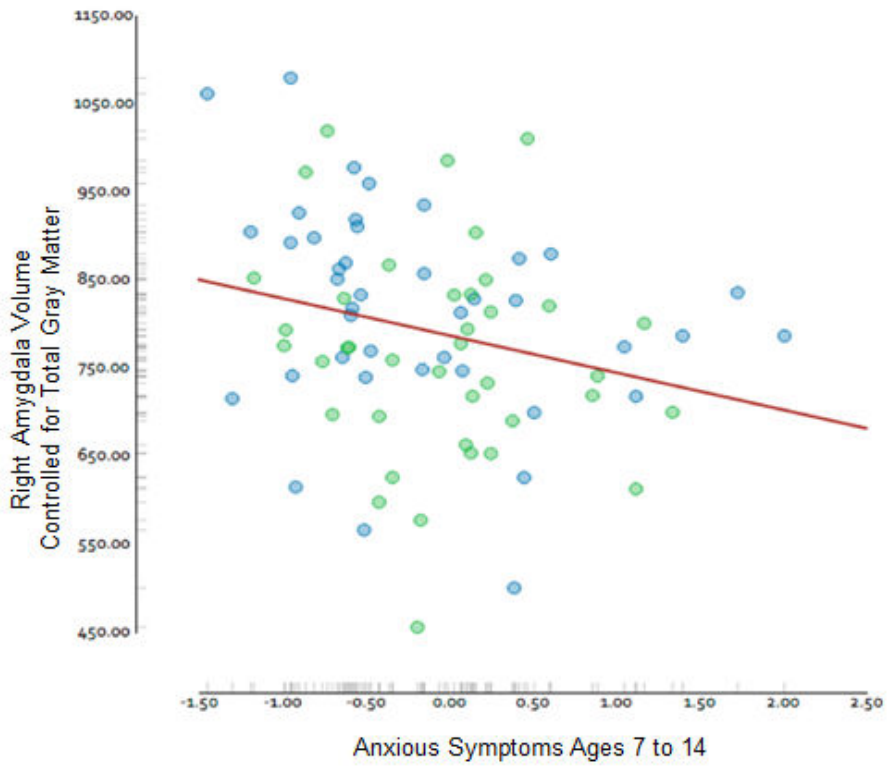

Figure 2: Anxious symptoms as measured by the MacArthur Health and Behavior Questionnaire (Essex et al., 2002) from age 7 to age 14 predict smaller right amygdala volume when controlling for total gray matter (p = 0.029). Males are represented with blue dots, females with green dots.

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