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Anxiety modulates the relation between attention-deficit/hyperactivity disorder severity and working memory-related brain activity

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Abstract

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Objectives—Individuals with attention-deficit/hyperactivity disorder (ADHD) often have heightened levels of anxiety, which has been associated with worse performance on working memory tasks. Knowledge of the neural pathways underlying the combined presence of ADHD and anxiety may aid in a better understanding of their co-occurrence. Therefore, we investigated how anxiety modulates the effect of ADHD severity on neural activity during a visuospatial working memory (VSWM) task.

Methods—Neuroimaging data was available for 371 adolescents and young adults participating in the multicentre cohort study NeuroIMAGE (average age 17.1 years). We analysed the effects of ADHD severity, anxiety severity, and their interaction on task accuracy, and on neural activity associated with working memory (VSWM trials minus baseline), and memory load (high memory load trials minus low load trials).

Results—Anxiety significantly modulated the relation between ADHD severity and neural activity in the cerebellum for the working memory contrast, and bilaterally in the striatum and thalamus for the memory load contrast.

Conclusions—We found that ADHD with co-occurring anxiety is associated with lowered neural activity during a VSWM task in regions important for information gating. This fits well with previous theorizing on ADHD with co-occurring anxiety, and illustrates the neurobiological heterogeneity of ADHD.

Keywords

Attention Deficit Hyperactivity Disorder; Anxiety; Working Memory; Magnetic Resonance Imaging; Comorbidity

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is associated with heightened levels of anxiety; up to 50 percent of individuals with ADHD have one or more comorbid anxiety disorders (Schatz and Rostain 2006; Yoshimasu et al. 2012). Higher rates of anxiety disorders are found in both clinical and epidemiological samples of individuals with ADHD, even when controlling for overlap in symptomatology (Angold, Costello, and Erkanli 1999; Pliszka 2000). Given reports of significant effects of co-occurring anxiety on the cognitive functioning of individuals with ADHD (Bloemsma et al. 2013), their clinical presentation (March et al. 2000), and response to medication (M. T. A. Cooperative Group 1999; Bedard and Tannock 2008; Tannock, Ickowicz, and Schachar 1995), some authors have suggested that ADHD with comorbid anxiety represents a distinct subtype of ADHD (Jensen, Martin, and Cantwell 1997).

Visuospatial working memory (VSWM) tasks are well suited to investigate how co-occurring anxiety may influence ADHD-related cognitive impairments. Impaired working memory is a core cognitive deficit in ADHD, with strongest deficits in VSWM (Martinussen et al. 2005). Working memory is also a strong determinant of functional outcomes such as academic achievement (Rennie, Beebe-Frankenberger, and Swanson 2014), which makes it an important research target. Cognitive interference theories predict that high levels of anxiety have adverse effects on the performance of cognitive tasks, as irrelevant thoughts

may interfere with information processing (Sarason 1984). Anxiety has been rather inconsistently associated with lowered VSWM performance (Shackman et al. 2006; Aronen et al. 2005; Staugaard 2010), but has also been reported to interact with working memory capacity, such that only individuals with low capacity showed a negative relation between anxiety level and task performance (Owens et al. 2014). Given that ADHD is associated with impaired working memory, such findings suggest that anxiety may be particularly detrimental if co-occurring with ADHD. This is in accordance with several reports that individuals with ADHD and comorbid anxiety are less accurate on working memory tasks than those who have ADHD without anxiety (Jarrett et al. 2012; Bedard and Tannock 2008; Skirbekk et al. 2011; Pliszka 1989), although these findings have not always been replicated (Vance et al. 2013; Manassis et al. 2007).

Neuroimaging data may provide a more sensitive and informative measure of working memory impairments than data on behavioural performance. VSWM is primarily associated with activity of frontoparietal brain regions, in line with the role of these regions in executive functioning and spatial awareness (Curtis 2006). Longitudinal studies of VSWM capacity have further shown that its development is associated with increased neural activity and connectivity of these frontal and parietal, as well as striatal, regions (Darki and Klingberg 2014). The few functional magnetic resonance imaging (fMRI) studies on the relation between ADHD and VSWM have not produced a clear pattern of results, as they reported either higher or lower activity of these neural circuits in individuals with ADHD compared to controls, or no differences at all (Li et al. 2014; Vance et al. 2007; Silk et al. 2005; van Ewijk et al. 2015). Anxiety has been associated mostly, though also inconsistently, with heightened activity in frontal regions during working memory, particularly the dorsolateral prefrontal cortex (DLPFC) (Fales et al. 2008; Park et al. 2016; Denkova et al. 2010; Moon and Jeong 2015; Basten, Stelzel, and Fiebach 2012). To our knowledge, no study to date has investigated whether ADHD and anxiety interact on working-memory related brain activity.

We hypothesized that the neurobiological pathways underlying anxiety severity co-occurring with symptoms of ADHD may differ from those that have been found for anxiety or ADHD severity when studied separately, thereby contributing to the large heterogeneity observed in behavioural and neuroimaging studies. Because of these possible differences, we did not restrict our analyses to brain regions commonly reported to be associated with ADHD or anxiety but employed a whole-brain approach. We carried out the analyses in an adolescent and young adult sample (mean age 17.1 years) consisting of individuals with ADHD, individuals with subthreshold ADHD, and healthy comparison subjects, thus enabling analysis within a wide range of ADHD severity in accordance with the continuous distribution of ADHD within the population (Levy et al. 1997).

Method

Participants and protocol

Participants were selected from the NeuroIMAGE study, a follow-up of the Dutch part of the International Multicenter ADHD Genetics (IMAGE) study (von Rhein et al. 2014). NeuroIMAGE included 365 families with at least one child with ADHD and at least one

biological sibling (regardless of ADHD diagnosis) and 148 control families with at least one child without any formal or suspected ADHD diagnosis in any of the family members or their first-degree relatives. To be included in NeuroIMAGE, participants had to be of European Caucasian descent, between ages 5 and 30 years, have an IQ ≥ 70 , and have no diagnosis of autism, epilepsy, general learning difficulties, brain disorders, or known genetic disorders. The study was approved by the regional ethics committee (CMO Regio Arnhem – Nijmegen; 2008/163; ABR: NL23894.091.08) and the medical ethical committee of the VU University Medical Center. All participants, and their parents (if the participant was younger than 18 years), signed informed consent; parents signed informed consent for participants under twelve years of age.

For the analyses reported in this paper, 371 participants, from 234 families, had complete data. Of the 371 participants, 122 participants had an ADHD diagnosis, 49 participants had subthreshold ADHD (i.e., had elevated levels of ADHD symptoms without meeting the full criteria for an ADHD diagnosis), and 200 participants were healthy controls. ADHD diagnoses were made in accordance with DSM 5 criteria, on the basis of a combination of a semi-structured interview and the Conners Rating Scales (Conners et al. 1998). Of those with an ADHD diagnosis, 93 (76%) had a history of treatment with stimulant medication. Sixteen (33%) of those with subthreshold ADHD and one healthy control (0.5%) had a history of receiving stimulant medication. Participants were asked to withhold use of their stimulant medication or other psychoactive drugs for 48 hours before measurement. Mean age of this sample was 17.1 years (standard deviation (SD) 3.4), ranging from 7.7 to 29.2 years, with the 10th and 90th percentiles being 13.1 and 21.4 years. 52.3% of the sample was male. More information on the NeuroIMAGE study, its diagnostic algorithm, and its participants, is presented in the Supplementary Information (SI) and in von Rhein et al. (2014).

ADHD outcome measure

In order to retain as much information as possible, we used a continuous measure of ADHD severity, the raw score on subscale N of the Conners Parent Rating Scale (CPRS) (Conners et al. 1998). This score ranged from 0 to 53, with an average of 11.3 (SD 11.5). This measure was chosen because it was available for all participants, from both ADHD families and control families.

Anxiety outcome measure

Anxiety severity was measured with the emotion subscale of the Strengths and Difficulties Questionnaire (SDQ-E) (Goodman 2001). The SDQ is well validated, has good internal consistency, and is reliable across informants and time (Achenbach et al. 2008). It has been shown to be a good dimensional measure of psychopathology in children, with the odds of a psychiatric disorder increasing at a constant rate across the range of scores (Goodman and Goodman 2009). The emotion subscale contains the following items: “Many worries, often seems worried”, “Often unhappy, down-hearted or tearful”, “Often complains of headaches, stomach-aches or sickness”, “Nervous or clingy in new situations, easily loses confidence”, and “Many fears, easily scared”. Ratings on the emotion subscale have been shown to be associated with the presence of common comorbid anxiety disorders, but not depression in

an ADHD sample (Bekker, Bruck, and Sciberras 2013). Each item was rated both by the participant (if older than 12 years of age) and a parent on a three-point scale (“not true” (0), “somewhat true” (1), “certainly true” (2)). In order to gain maximum sensitivity to often underreported anxiety symptoms (Pliszka 1992), we selected the highest of either of the two informants’ scores on each item and subsequently summed these five highest item scores together, for a minimum of 0 and a maximum of 10. The average score for the whole sample was 4.16 (SD 2.03). Additional information on the composition of this measure is given in SI, as well as an overview of the scores per item and per informant.

Socio-economic status

As a measure of socio-economic status (SES), the highest, successfully completed education level of the parents was re-coded into a measure reflecting years of education. This scale contained nine levels, ranging from 0 (no formal education) to 17 (university) years of education (Buis 2010). The average of both parents was used, which, in this sample, ranged from 5 to 17 with an average of 12.2 (SD 2.47).

Visuospatial working memory task

To measure VSWM, we used a spatial span task (Klingberg, Forssberg, and Westerberg 2002) described more fully elsewhere (van Ewijk et al. 2014). The task consisted of two trial types (baseline and working memory) and two memory loads (low and high). In working memory trials, either three (low load) or six yellow circles (high load) were sequentially displayed on a 4×4 grid for 500 ms, with a 500 ms inter-stimulus interval. This was followed by a 2000 ms response window, during which the participant was asked whether a probe, consisting of a question mark and a number, was presented in the correct spatial location and the right temporal order of the presentation of cues, as indicated by the number. Participants answered by pressing one of two buttons representing ‘yes’ and ‘no’. We also included baseline trials for the low and high memory load conditions, both consisting of sequentially presented red circles in the four corners of the grid, followed by a probe (always the number 8). Participants were asked to pay attention but not to try to remember the sequence, and to press the ‘no’ button. Feedback on all trials was presented after the response in the form of a green or red coloured bar below the probe (for correct and incorrect responses, respectively). Accuracy on all trial types was determined as percentage correct responses. The task consisted of 4 blocks of 24 trials each, presented in fixed random order, for a total time of approximately 16 minutes.

fMRI analysis

Details on fMRI data acquisition, handling of runs with excessive head motion, and preprocessing are given in SI.

For the within-run analyses, we constructed a general linear model containing regressors for each of the four types of trial (i.e. low and high memory load, for both working memory and baseline trials), modelled from the start of the trial to the onset of the probe, in accordance with the approach by Klingberg et al. (2002). We also included regressors for feedback on correct and incorrect trials in the model, to remove unexplained variance. Further, global signal from cerebral spinal fluid and white matter, and standard and extended motion

parameters were included as nuisance covariates. Beta-maps from all runs were concatenated using a single-subject fixed effects model, and the resulting maps were transformed to a study-specific template. Our contrasts of interest were *mean working memory* (both memory loads averaged, working memory trials minus baseline trials) and *memory load difference* (high minus low memory load trials), both consisting of the regressors for working memory trials corrected for regressors of the baseline trials of the same load.

Whole-brain analysis was conducted with the use of a variant of FSL's 'randomise' algorithm, which employs nonparametric permutation inference (Winkler et al. 2015). To take into account the family relatedness present in the sample, we specified exchangeability blocks based on family membership, which ensured that only the rearrangements of the data that respect exchangeability were used (Winkler et al. 2015). The main model consisted of ADHD severity, anxiety severity, their interaction, and age, sex, socio-economic status, and scanning location as additional covariates. All regressors were mean-centred. The data were permuted 5000 times. We used cluster mass-based inference, with an initial cluster-forming threshold of $z=2.3$. We set the whole brain family-wise error rate corrected p-value at $p < .01$ to correct for the fact that we were looking at whole-brain maps for both the working memory contrast and memory load contrast.

Analysis of task accuracy and cluster data

All additional analyses were performed in R, v3.1.1, with linear mixed effects models. We estimated a random intercept for family, i.e. the intercept was allowed to vary between families, to account for the non-independence of the observations due to the inclusion of siblings in the sample. The linear mixed effects model included memory load (high and low load) as a within-subject factor, and accuracy on baseline trials as a covariate to control for basic processing or motivational effects. All models had age, sex, socio-economic status, and scanner location included as covariates. All continuous variables were standardized, because they were measured on widely differing scales.

“ In a second set of analyses, we assessed the effects of memory load by adding interaction terms between memory load condition (low or high load) and the predictors of interest (ADHD, anxiety, and their interaction) to the initial model.”

We further extracted the mean signal from significant clusters from the whole-brain analysis and calculated Cohen's f^2 as a measure of effect size for the significant predictors, as shown in Table 1. As a post-hoc analysis, we also ran a mixed effects repeated measures model where working memory task accuracy was regressed on the cluster data, corrected for baseline accuracy, in order to couple our results at the neural level to task performance.

Sensitivity analyses

Because of our dimensional approach to studying ADHD and its interaction with anxiety, we report demographic information on the participants split by ADHD diagnostic status in the SI. We further checked whether the findings were influenced by scanning location, by adding an interaction term between testing location and our predictors of interest and reran the analysis on the data from clusters found to be significant in the main analysis. In

addition, while stimulant medication was discontinued 48h before measurement, we also reran the analyses with a covariate for duration of stimulant medication use, in the subset of individuals with an ADHD diagnosis.

Results

Task accuracy

ADHD severity was associated with lower accuracy on the VSWM task, independent of anxiety ($b=-0.10$, $SE=0.05$, $p=.04$), in accordance with a previous report on a subsample used in this study (van Ewijk et al. 2014). There was no conditional main effect of anxiety severity ($b=-0.05$, $SE=0.04$, $p=.26$), nor did anxiety severity modulate the effect of ADHD severity on working memory task accuracy ($b=0.01$, $SE=0.03$, $p=.77$). See Table S2 for the full results.

Memory load was a highly significant predictor of accuracy ($b=-0.45$, $SE=0.06$, $p<.001$), with the average accuracy on low load working memory trials being 79.2% versus 74.3% at high load, confirming the success of the task manipulation. Memory load did not significantly modulate the effect of ADHD severity, anxiety severity, or their interaction, on task accuracy (all $p>.19$).

Neural activity for mean working memory contrast

The mean working memory contrast was associated with widespread brain activity across superior and middle frontal gyri, superior parietal cortex, thalamus, striatum, and cerebellum. Further information on these clusters is provided in SI.

We found ADHD severity to be negatively correlated with working memory-associated brain activity in the left frontal pole. There was no conditional main effect of anxiety severity, but anxiety did modulate the relation between ADHD severity and brain activity in the right cerebellum, such that it correlated positively with ADHD severity for individuals with low levels of anxiety and negatively for individuals with high levels of anxiety (Figure 1). More information on these clusters is reported in Table 1. Figure 2a shows the location of these clusters overlaid on the sample's average anatomical image.

Neural activity for memory load difference contrast

Anxiety severity modulated the association of ADHD severity with brain activity bilaterally in the dorsal striatum and thalamus for the memory load difference contrast. Individuals with high anxiety had a negative correlation between ADHD severity and task difficulty-associated brain activity, whereas those with low anxiety displayed a positive slope (Figure 3). Further information on these clusters is reported in Table 1 and Figure 2b. Post-hoc analysis showed that task accuracy was significantly positively correlated with the mean values of these clusters for the memory load difference contrast ($b=0.17$, $SE=0.05$, $p<.001$). In other words, an increase of basal ganglia activity when the task became more difficult was associated with higher task accuracy.

Sensitivity analyses

Results from the sensitivity analyses can be found in SI. There were no interaction effects between the predictors of interest and testing location on brain activity in the significant clusters. Further, the predictors found to be significant in the main analyses remained significant when treatment duration was added as a covariate.

Discussion

We aimed to investigate whether anxiety modulates the association between ADHD severity and neural correlates of VSWM. Such interaction effects would indicate that previously reported differences in working memory performance between people with ADHD with and without comorbid anxiety (Jarrett et al. 2012; Bedard and Tannock 2008; Skirbekk et al. 2011; Pliszka 1989) cannot be attributed solely to additive effects of ADHD and anxiety, and illustrate that their co-occurrence carries significant information that may aid in explaining some of the etiological and phenotypic heterogeneity typical of ADHD research. We found that anxiety severity modulates the association between ADHD severity and brain activity in the cerebellum, basal ganglia and thalamus.

In our sample, ADHD severity was associated with lowered accuracy on VSWM task performance (see also van Ewijk et al. 2014), in accordance with meta-analyses (Martinussen et al. 2005; Willcutt et al. 2005). We also replicated a previous finding of a negative relation between ADHD severity and activity in frontal brain regions underlying VSWM (Silk et al. 2005). Specifically, we found less activity in the left frontal pole and superior frontal gyrus, which are known to respond more to spatial tasks than to object-based tasks (Courtney et al. 1996), when working memory must be continuously updated, and when temporal order must be maintained (Wager and Smith 2003), as was the case in our task. Further, these effects were independent of co-occurring anxiety.

While cognitive interference theories state that anxiety causes irrelevant information to interfere with task performance (Sarason 1984), we did not find effects of anxiety on VSWM brain activation or performance. Eysenck *et al.* theorized that the worrying of anxious individuals can lead to lowered performance on cognitive tasks by occupying resources, but that this is partly compensated by greater on-task effort (Eysenck and Calvo 1992). This may cause the negative effect of anxiety on working memory performance to only become apparent at higher difficulty levels, or in individuals with low working memory capacity as has been previously reported (Owens et al. 2014), rather than there being a direct relation between anxiety and cognitive functioning (Eysenck et al. 2007). The inconsistent results from previous behavioural and neuroimaging studies, as well as our null findings, attest to a complex relation between anxiety and working memory that is dependent on task and sample characteristics (Jarrett 2016).

Consistent with this reasoning, we did find that anxiety interacts with ADHD severity on neural activity. During the working memory task, higher levels of anxiety were associated with a more negative relation between ADHD severity and neural activity in the cerebellum. The cerebellum is increasingly recognized to be important for the development of cognitive functions (Riva and Giorgi 2000), including working memory (Ford et al. 2014), and has

been previously shown to be less active in individuals with ADHD compared to controls during working memory tasks (Valera et al. 2005; Massat et al. 2012). Its specific function during working memory has been characterized as that of a gatekeeper, based on findings that individuals with lesions in the cerebellum are more susceptible to interference by irrelevant information during tasks reliant on VSWM (Baier, Muller, and Dieterich 2014). Less cerebellar activity therefore could indicate that ADHD co-occurring anxiety is associated with lowered information filtering.

The interaction between ADHD and anxiety was further associated with less task difficulty-related brain activity in the caudate nucleus, putamen, and thalamus, supporting the notion that ADHD with co-occurring anxiety may involve lowered information filtering. Activity in the basal ganglia and thalamus during working memory has been shown to predict the extent to which only relevant information is stored, a strong determinant of working memory capacity (McNab and Klingberg 2008). Activation of the basal ganglia allows for the disinhibition of the thalamus and subsequent processing of stimuli for working memory (Gisiger and Boukadoum 2011). Information filtering should become more important with increasing task difficulty, as higher amounts of information may become overwhelming and reduce performance. Results from our post hoc analyses are consistent with this reasoning, as basal ganglia activity due to increased memory load was associated with higher task accuracy. Further, it is also in line with Levy's theory of ADHD with comorbid anxiety, which states that divergent gating of the basal ganglia leads to increased detection of threatening stimuli, contributing to feelings of anxiety (Levy 2004). The important role of dopamine in this process (Grace et al. 2007) conceivably plays a role in the repeatedly reported finding that individuals with ADHD with comorbid anxiety respond less well to stimulant medications than those without comorbid anxiety (Pliszka 1989; M. T. A. Cooperative Group 1999; Tannock, Ickowicz, and Schachar 1995).

We did not find evidence that anxiety modulates the relation between ADHD severity and task performance. Findings from studies into the relation between working memory performance and ADHD with comorbid anxiety have been mixed, with some reporting significant differences (Jarrett et al. 2012; Bedard and Tannock 2008; Skirbekk et al. 2011; Pliszka 1989) and others reporting null findings (Vance et al. 2013; Manassis et al. 2007). This inconsistency may be partly due to differences in task characteristics between studies; our findings on brain activity associated with varying memory load described above suggest that particularly task difficulty may be an important factor in outcomes of neuropsychological research of ADHD with co-occurring anxiety; problems with information gating may only be captured by measures of task performance when the stimulus rate increases and the information flow gets too high to adequately process. We therefore speculate that at higher task difficulties than present in the current study, less activity of the basal ganglia and cerebellum associated with the interaction between anxiety and ADHD severity may also be associated with overt performance difficulties on working memory tasks.

Strengths of this study include a large sample size and use of dimensional measures, allowing for optimal detection of effects. Furthermore, to our knowledge, we are the first to investigate the effects of ADHD co-occurring anxiety at the neural level, thereby providing

information on its neurobiological correlates. The foremost limitation is the observational, cross-sectional design of our study, which prevents strong inferences about any causal relationship between the developmental course of ADHD, anxiety, and the brain. One might also argue that our measure of anxiety is not entirely specific to anxiety, but also measures depression. However, in ADHD samples, this instrument was found to only significantly relate to commonly occurring comorbid anxiety disorders, and not to mood disorders (Bekker, Bruck, and Sciberras 2013), see also SI. Further, due to our recruitment strategy of healthy controls, our sample has limited variation in anxiety in individuals with low ADHD severity, restricting the interpretation how these findings relate to individuals with pure anxiety. Therefore, also given that we are the first to report on the neural correlates of ADHD co-occurring anxiety, future studies in independent samples are needed to replicate our findings. Particularly fMRI studies using tasks that strongly engage the limbic system and experimental studies that manipulate the dopaminergic system may be valuable, to more directly test whether divergent information gating is a key factor in ADHD co-occurring anxiety.

In conclusion, we found that ADHD with co-occurring anxiety is associated with patterns of brain activity beyond the additive effects of ADHD and anxiety. This indicates that the combined presence of symptoms of ADHD and anxiety may be due to partly different neurobiological correlates than either separately. Given their common co-occurrence, these interaction effects may form a source of heterogeneity that contributes to inconsistent findings in studies of ADHD and anxiety. The involvement of brain regions important for gating of information could suggest that measures of the combined presence of ADHD and anxiety may capture problems with filtering of information, in line with Levy's biological theory of ADHD with comorbid anxiety (Levy 2004), whereas at lower levels of anxiety, other mechanisms may be at play that contribute to any negative relation between ADHD severity and working memory performance. Further research on the neurobiological correlates of ADHD and co-occurring anxiety may not only aid in resolving some of the heterogeneity of ADHD, but ultimately also have clinical implications by enabling a more effective treatment tailored to the individual's profile (M. T. A. Cooperative Group 1999).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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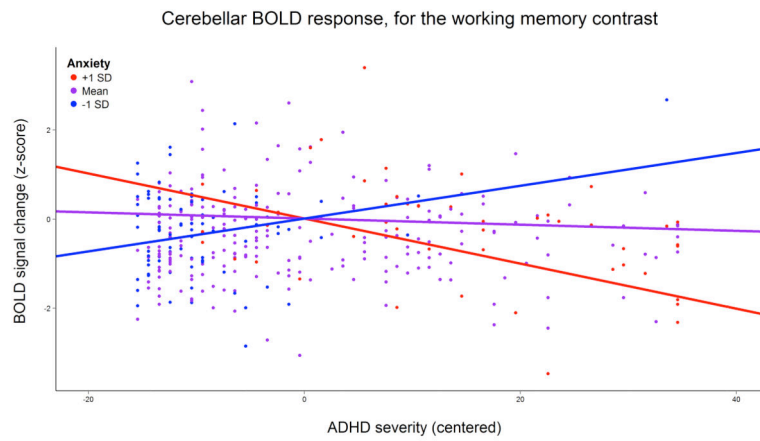


Figure 1. Modulating effect of anxiety severity on the association between ADHD severity and blood-oxygen dependent level (BOLD) signal change in the cerebellum while subjects performed the visuospatial working memory task. The x-axis reflects the score on the Conners' Parent Rating Scale. Regression lines indicate effect of ADHD severity for average anxiety severity (purple line), as well as one standard deviation (SD) above (blue line) and one SD below average anxiety severity (red line).

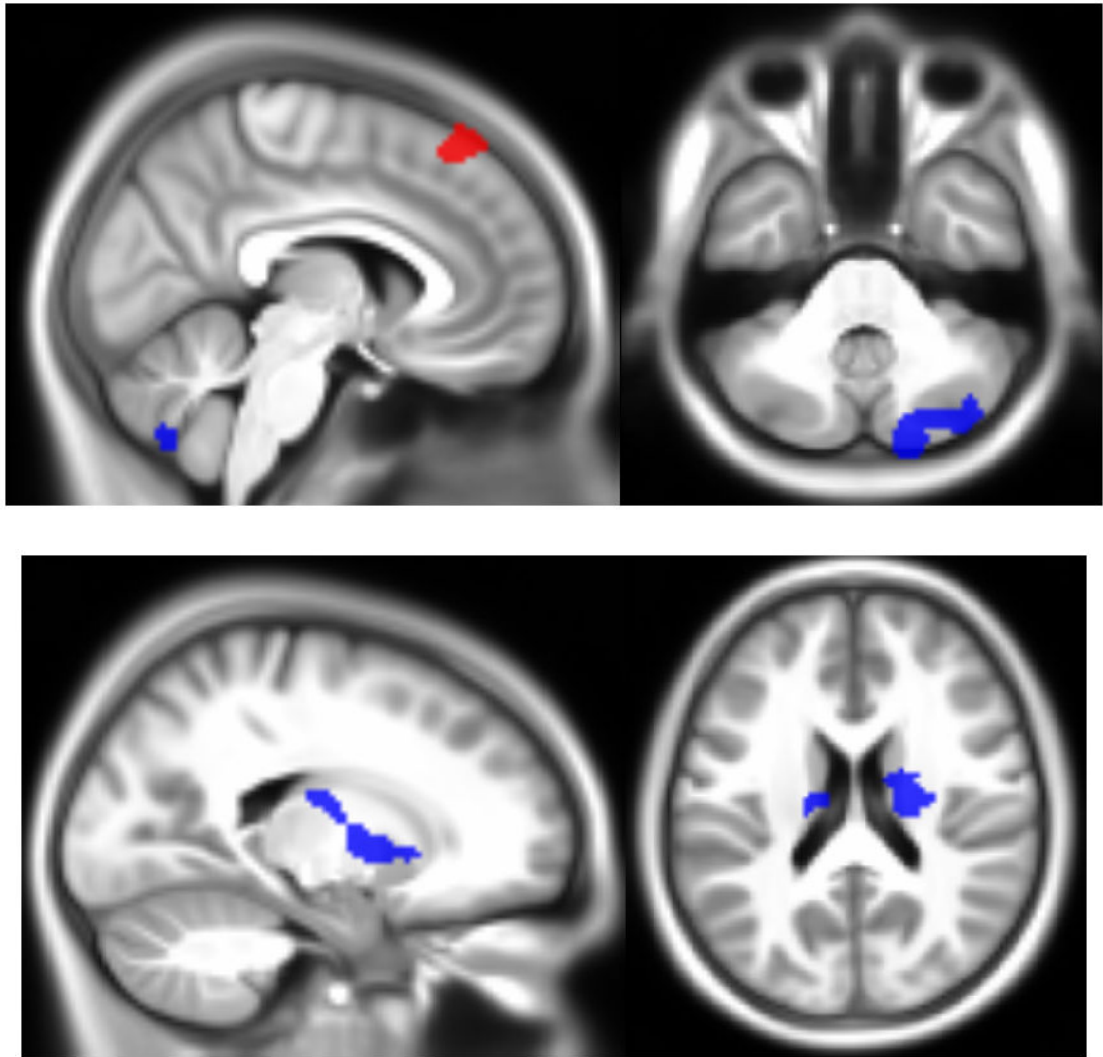


Figure 2. Location of the clusters surviving multiple comparison correction at $P < .01$, overlaid onto the sample's average anatomical image. The top part ($X=6$, $Y=-60$, $Z=-36$) shows where there was an effect of ADHD severity (red) and the interaction between anxiety and ADHD (blue) on brain activity for the mean working memory contrast; the bottom part ($X=-20$, $Y=-10$, $Z=20$) shows the clusters with a significant effect of the interaction between anxiety and ADHD for the memory load difference contrast.

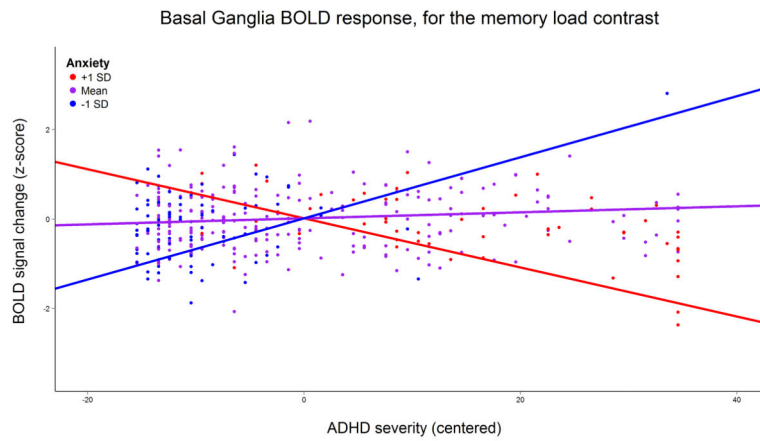


Figure 3.

Graph of the mean blood-oxygen level dependent (BOLD) signal change at the clusters in the striatum and thalamus (clusters combined), for the memory load contrast. Regression lines indicate effect of ADHD severity for average anxiety severity (purple line), as well as one standard deviation above (blue line) and below (red line) average anxiety severity.

Summary of the clusters that showed a significant correlation ($P_{FWE} < 0.01$) between brain activity and the predictors. The upper part of the table shows the clusters correlating with activity for the mean working memory contrast, the bottom part of the table shows those associated with memory load.

Table 1

Mean working memory							
Contrast	Direction	Region	X	Y	Z	Size	Z_{max} Cohen's d^2
ADHD	Negative	L Frontal Pole, Superior Frontal Gyrus	-4	42	56	918	4.09 .011
Anxiety	N/A						
ADHD * Anxiety	Negative	R Cerebellar Crus I, Crus II VIIIa	18	-88	-34	762	3.54 .028

Memory load difference							
Contrast	Direction	Region	X	Y	Z	Size	Z_{max} Cohen's d^2
ADHD	N/A						
Anxiety	N/A						
ADHD * Anxiety	Negative	R Thalamus, Caudate, Putamen	12	-18	16	682	4.46 .047
	Negative	L Thalamus, Caudate, Putamen, Pallidum	-20	0	0	516	3.93 .055

Note: X, Y, Z coordinates are in MNI-space in mm, and represent the peak of the cluster. The anatomical labels are according to the Harvard-Oxford atlas. MNI=Montreal Neurological Institute; Z_{max} = Z-score at the peak of the cluster.