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Altered striatal intrinsic functional connectivity in pediatric anxiety

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Abstract

Anxiety disorders are among the most common psychiatric disorders of adolescence. Behavioral and task-based imaging studies implicate altered reward system function, including striatal dysfunction, in adolescent anxiety. However, no study has yet examined alterations of the striatal intrinsic functional connectivity in adolescent anxiety disorders.

The current study examines striatal intrinsic functional connectivity (iFC), using six bilateral striatal seeds, among 35 adolescents with anxiety disorders and 36 healthy comparisons.

Anxiety is associated with abnormally low iFC within the striatum (e.g., between nucleus accumbens and caudate nucleus), and between the striatum and prefrontal regions, including subgenual anterior cingulate cortex, posterior insula and supplementary motor area.

The current findings extend prior behavioral and task-based imaging research, and provide novel data implicating decreased striatal iFC in adolescent anxiety. Alterations of striatal neurocircuitry identified in this study may contribute to the perturbations in the processing of motivational, emotional, interoceptive, and motor information seen in pediatric anxiety disorders. This pattern of the striatal iFC perturbations can guide future research on specific mechanisms underlying anxiety.

Keywords

Anxiety; Adolescence; Neuroimaging; Resting state fMRI; Reward; Striatum

1. Introduction

Anxiety disorders are among the most common psychiatric disorders of adolescence (Beesdo et al., 2009; Costello et al., 2003; Kashani and Orvaschel, 1990; Merikangas et al., 2010). Behavioral and task-based imaging studies implicate alterations of reward system, including striatal dysfunction, in adolescent anxiety. Since the striatum is a key node of the circuits that support motivated behavior, such as incentive valuation, motivation, learning,

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and motor control, the next logical step would be to examine the functional connectivity of this structure with both cortical and subcortical structures implicated in pediatric anxiety. Resting state functional neuroimaging analysis is a powerful method to illuminate the functional connectivity of the striatal circuits. The current study is the first study to our knowledge to use resting state functional neuroimaging to assess differences in striatal intrinsic functional connectivity (iFC) between healthy adolescents and adolescents with anxiety.

Adolescence is a high-risk period for the emergence of anxiety disorders (Beesdo et al., 2009), possibly due to transformative developmental changes in brain function, including the maturation of the reward system (Ernst, 2014; Spear, 2000; Steinberg, 2005). Recent work links adolescent anxiety to alterations in reward-system function. Behaviorally, anxious youths tend to be less motivated by reward (Hardin et al., 2007; Jazbec et al., 2005; Richards et al., 2015) and more risk averse (Lorian and Grisham, 2010; Lorian et al., 2012a, 2012b; Maner and Schmidt, 2006). In task-based neuroimaging studies, anxious relative to non-anxious youths tend to exhibit greater activation in the striatum, a key node of the reward system. A similar pattern has been observed in adolescents at-risk for developing an anxiety disorder (Bar-Haim et al., 2009; Guyer et al., 2006). We hypothesized that altered task-related activation of the striatum in anxiety could reflect alterations in intrinsic functional connectivity of striatal network.

Task-related activation is classically interpreted as higher neuronal firing during task than baseline (Hulvershorn et al., 2014). In contrast, intrinsic functional connectivity between two regions refers to the degree of coherence in the spontaneous activity between these regions (Hulvershorn et al., 2014; Buxton, 2013) as well as a reflection of the history of co-activation of brain regions engaged in the same information processing pathway (Guerra-Carrillo, 2014). Granted that the measures of activation and connectivity reflect different functional metrics, we reason that if one functional aspect is abnormal, there is a high likelihood that another related functional aspect is also abnormal. Along these lines, abnormally high neuronal activity of the striatum might coexist with abnormal connectivity across striatal regions. Therefore, the object of this study is to examine alteration in striatal intrinsic functional connectivity in pediatric anxiety. To our knowledge, this is a first study of such study in pediatric anxiety.

The striatum is composed of three main nuclei: the nucleus accumbens (NAcc), caudate nucleus, and putamen (Alexander et al., 1986; Parent and Hazrati, 1995). These nuclei form hubs in a series of parallel striato-thalamo-cortical pathways to serve emotional, cognitive and sensorimotor functions (Alexander et al., 1986; Parent and Hazrati, 1995). These loops are functionally organized along a ventral-dorsal topography (Alexander et al., 1986; Ernst and Fudge, 2009; Parent and Hazrati, 1995), with ventral regions supporting emotional/motivational processes and dorsal regions supporting cognitive and motor functions (Haber and Knutson, 2010). Anxiety symptoms might be associated with changes in both ventral and dorsal striatal circuits due to the emotional/motivational (e.g., risk aversion) and cognitive perturbations (e.g., attention bias) associated with anxiety. The present study uses resting state fMRI with ventral and dorsal striatal seeds, previously characterized in healthy

subjects (Di Martino et al., 2008), to compare striatal iFC between healthy and clinically anxious adolescents.

While no studies have yet examined striatal iFC in anxious youths, two studies in anxious adults have recently been published (Arnold Anteraper et al., 2014; Manning et al., 2015). Both studies focused on social anxiety disorder, and the findings were somewhat divergent. One study (Arnold Anteraper, Triantafyllou et al., 2014) revealed consistently stronger striatal iFC with cortical regions in the anxious vs. healthy group. The other study (Manning et al., 2015) only examined iFC of the ventral striatum, specifically the NAcc, and found both abnormally high and abnormally low iFC in SAD adults. Importantly, both studies confirmed widespread differences in striatal iFC in clinically anxious vs. healthy adults.

Based on these previous studies in adults, we predicted differences in striatal iFC between anxious and healthy adolescents, but the direction of these differences was difficult to anticipate for two reasons. First, findings in adults were not all consistent, and second, the adolescent brain continues to mature, with documented developmental differences in striatal connectivity relative to the adult brain (Ernst, 2014; Ernst et al., 2006; Porter et al., 2015). We also expected that anxiety would affect both ventral and dorsal components of striatal iFC, as well as within striatal networks and between striatum and prefrontal networks.

2. Methods and materials

2.1. Participants

Thirty five (21 females; mean age 13.2 years) youths diagnosed with an anxiety disorder were compared with 36 healthy youths (21 females; mean age 13 years). This study was approved by the National Institute of Mental Health Institutional Review Board. After receiving a thorough explanation of the study, subjects signed an informed assent and their parents an informed consent. All subjects were paid for their participation.

All subjects were assessed medically via a clinical interview and physical exam, and psychiatrically via the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (Kaufman et al., 1997), administered by experienced clinicians trained to achieve satisfactory inter-rater reliability ($k > 0.75$) with expert diagnosticians. Inclusion criteria for all subjects were (1) age of 8–18 years, (2) IQ > 70 (the lowest IQ was 83), (3) absence of any psychoactive agent, and (4) absence of acute or chronic medical problems. Further inclusion criteria for healthy subjects were the absence of any current or past psychiatric disorders and, for anxious patients, a primary diagnosis of an anxiety disorder, a Pediatric Anxiety Rating Scale score > 9 (Birmaher et al., 1997), and a desire for outpatient treatment. Exclusion criteria for this study were current Tourette's syndrome, obsessive–compulsive disorder, posttraumatic stress disorder, and conduct disorder, exposure to extreme trauma, suicidal ideation, and lifetime history of mania, psychosis, or pervasive developmental disorder.

IQ was measured using the vocabulary and matrix reasoning subscales of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). Socioeconomic status was obtained through parental report and calculated on the basis of the Hollingshead's index of social

position for education and employment (Hollings-head, 1975). Additional behavioral measures included the Screen for Anxiety Related Disorders (SCARED) (Birmaher et al., 1997) parent and child questionnaire (the average of the child and parent responses was used for all analyses, SCARED-pc), the Behavioral Inhibition and Activation Scales (BIS/BAS scales) (Carver and White, 1994), Children's Depression Inventory (CDI) (Kovacs, 1985), and the Fear of Negative Evaluation (FNE) (Watson and Friend, 1969). The SCARED and BIS/BAS questionnaires provide a total score and subscale scores. The SCARED questionnaire provides sub-scores for Panic Disorder, Generalized Anxiety Disorder (GAD), Separation Anxiety, Social Anxiety, and School Avoidance. The BIS/BAS is composed of two subscales: Behavioral Inhibition System (BIS) and Behavioral Activation System (BAS). The BAS is further subdivided into 3 sub-scales: Reward Responsiveness (Reward), Drive, and Fun Seeking.

2.2. Image acquisition

MR images were acquired using four General Electric 3T scanners. Resting state fMRI scans were acquired while participants passively viewed a fixation cross for 6 min with dimmed lighting. Blood oxygen-level dependent (BOLD) signal was measured by echoplanar imaging (EPI) with the same parameters across scanners: flip angle=90°, echo time=30 ms, repetition time=2.0 s, 180 volumes, field of view=192 mm, and acquisition voxel size=3 × 3 × 4 mm³. For anatomic registration and spatial normalization, high resolution T¹-weighted MPRAGE anatomical images were collected using standardized magnetization prepared spoiled gradient recalled echo sequence: 124 1.2 mm thick axial slices, 7.816 repetition time, 3.024 echo time, 6° flip angle, 256 × 192 matrix, and 22 cm field of view.

2.3. Image processing

All images were processed using the Analysis of Functional Neuroimages (AFNI) resting state image processing stream that included ANATICOR (Jo et al., 2013) to minimize the effect of physiological and hardware noise. Motion parameters did not differ significantly among groups (see Table 1).

Prior to processing, EPI images were inspected for gross artifacts and gross motion. Subjects with gross motion exceeding 3 mm were excluded from further analysis. Preprocessing procedures were closely based on processing stream developed by AFNI (Jo et al., 2013). EP images were processed by excising the first four volumes, de-spiking, correcting for slice timing, volume registering and aligning to a Talairach template, and smoothing using a 6-mm full-width at half-maximum Gaussian kernel. With the goal of modeling noise for subsequent removal from the time series, processed images were then entered into a nuisance regression with the following parameters: a cubic de-trending polynomial, 12 motion parameters (the mean and derivatives for three translational and three rotational motion directions), bandpass filter parameters with limits of 0.01 and 0.1 Hz, and local white matter signal parameters derived from the ANATICOR method (Jo et al., 2013; Jo et al., 2010). Residuals from the nuisance regression were resampled to 3 mm isotropic and represented the neural BOLD signal used for seed connectivity analysis. Any EPI volume with a Euclidean mean of 0.25-mm shift from its preceding volume was censored from

regression along with its preceding volume. Therefore, subject-level exclusion for motion was based on the 0.25-mm censoring. Subjects with more than 15% censored TRs were excluded from analysis. All images were visually inspected for acquisition artifact and registration.

2.4. Seed region of interest (ROI) selection

We selected 6 bilateral striatal seeds as described by Di Martino (Di Martino et al., 2008). Seeds were each $3 \times 3 \times 3$ mm³ cube, and their central Talairach coordinates (x, y z in mm) were at [1]±7, 7, -2 for the nucleus accumbens (NAcc); [2]±8, 12, 6 for the ventral caudate (VC); [3]±11, 11, 14 for the dorsal caudate (DC); [4]±25, -1, 7 for the dorsal caudal putamen (DCP); [5]±22, -5, 11 for the dorsal rostral putamen (DRP); and [6]±19, 9, 3 for the ventral rostral putamen (VRP). Only the left NAcc seed was used for group analyses because of poor coverage of the right NAcc.

2.5. Single subject connectivity maps

For each participant, we applied seed masks to the resampled data to obtain time series for each seed ROI. Each extracted seed ROI time series was then used to calculate the correlations with every other voxel in the EPI residuals data in Talairach space to derive iFC maps. In preparation for group comparisons of Pearson correlations, the correlation values in the brain maps were transformed to z-scores using Fisher's r-to-z transformation.

2.6. Group analysis

Group-level analysis of each connectivity map was done by analysis of covariance (ANCOVA) using 3dMVM with the main factors being group (healthy and anxious), while controlling for sex (male or female), age, scanner and IQ. Results were thresholded voxel-wise at $p < 0.005$. Cluster correction was used to control for multiple tests across whole brain gray matter via 2-tailed 3dClustSim. Since bilateral seeds were not independent, we cluster-corrected for 6 seed analyses yielding a Bonferroni-corrected alpha level of 0.008 ($< 0.05/6$), and a cluster threshold of 58 voxels (1566 μ l) per map. To further understand the effects of groups on the significant clusters, the individual mean connectivity of each of these clusters was extracted, and group effects were examined more specifically using the IBM Statistical Package for the Social Sciences (SPSS) Statistics Desktop 22.0.

2.7. Exploratory analyses

The effects of various anxiety diagnoses were explored on the striatal functional connectivity. Since the most common diagnoses were Generalized Anxiety Disorder (GAD; $n=9$), Social Anxiety Disorder (SAD; $n=8$) and co-morbid GAD and SAD ($n=16$) (see below in Demographics), the mean connectivity for these diagnoses was calculated for each significant cluster in SPSS. Two patients with co-morbid GAD and major depressive disorder (MDD) were excluded from these comparisons.

Finally, exploratory correlations of individual connectivity (between each seed and significant clusters) with behavioral measures (SCARED-pc, BIS/BAS, FNE and CDI) for respective subjects were conducted for the whole sample and separately for healthy and

anxious subjects in SPSS. Correlation coefficients were then transformed into Fisher z-scores and compared between diagnostic groups.

3. Results

3.1. Demographics

As shown in Table 1, groups were matched on sex, age, IQ, SES, as well as motion during scanning (maximum displacement and percentage of TRs censored). As expected, the groups differed on the SCARED-pc ($t = -13.11$, ($p = 1.14 \times 10^{-17}$, $df = 49$)), CDI ($t = -7.66$, ($p = 7.4 \times 10^{-9}$, $df = 37$)), and FNE ($t = -6.77$, ($p = 2.3 \times 10^{-8}$, $df = 45$)) scores, which were significantly higher for the anxious than healthy group. The anxiety group comprised patients with various primary anxiety disorders. The most common diagnoses were generalized anxiety disorder (GAD; 31%), social anxiety disorder (SAD; 23%), and comorbid GAD and SAD (46%). In addition to the above diagnoses, 6 patients presented with co-morbid specific phobia (17%), and 7 patients with co-morbid separation anxiety disorder (20%). Overall, 22 (63%) patients had more than one anxiety diagnosis, and 5 (14%) had “other” comorbid disorders, such as ADHD, MDD or ODD.

3.2. iFC group comparison

Four striatal seeds showed iFC clusters that differed significantly between the healthy and anxious group (Table 2). These seeds included the left NAcc, the right and left DC, and the right VC. The significant clusters were in the striatum and in the pre-frontal cortex. Extraction of individual connectivity data indicated a consistent pattern, according to which all group differences reflected lower positive connectivity (or greater negative connectivity) in the anxious compared to healthy group (Figs. 1–3). These clusters are described below, organized by seeds.

The left NAcc exhibited a cluster significantly different between groups in the right head/body of the caudate nucleus (Fig. 1).

The right DC showed differential iFC with clusters in the posterior insula and subgenual anterior cingulate cortex (sgACC) (Fig. 2).

The left DC revealed a cluster within the supplemental motor area cortex, (BA6 and SMA) (Fig. 3). This cluster had its peak intensity in the left middle frontal gyrus and extended bilaterally into the right hemisphere.

The right VC showed a cluster in the right supplementary motor area cortex (SMA and BA6) (Fig. 3). This cluster remained circumscribed to the right hemisphere.

3.3. Exploratory analyses

3.3.1. Diagnoses—The mean connectivity for each significant cluster was compared for GAD, SAD and co-morbid GAD and SAD (see Supplementary Fig. 1) using one factor (diagnosis), three level (GAD, SAD, and comorbid GAD and SAD) ANOVA. No statistically significant differences or trends were detected among these diagnoses.

3.3.2. Behavioral correlates of iFC group differences

3.3.2.1. Whole sample behavioral correlates: As expected, across the whole sample, measures of internalizing symptoms (SCARED-pc, CDI, and FNE) were significantly negatively associated with iFC of those clusters that elicited group differences (see Table 3).

3.3.2.2. Anxious vs. healthy group comparison: Exploratory correlations between iFC and behavioral measures were compared between the anxious and healthy groups. The correlation of DC*Insula iFC with the SCAREDpc-GAD subscale differed significantly between the anxious and healthy group ($z_{\text{obs}} = 2.28$), due to a positive correlation for healthy participants ($r = 0.26$, $n = 34$, $p = 0.163$) and a negative correlation for anxious participants ($r = -0.30$, $n = 34$, $p = 0.104$) (Fig. 4 and Table 4). A similar trend was found for the SCAREDpc-GAD subscale with NAcc*Caudate iFC ($z_{\text{obs}} = 1.81$). In addition, NAcc*Caudate iFC showed group differences in correlations between connectivity and four additional behavioral measures (Table 4): CDI ($z_{\text{obs}} = -2.75$) and three of the BIS/BAS subscales (BIS $z_{\text{obs}} = 2.37$, Fun $z_{\text{obs}} = 1.97$, and Reward $z_{\text{obs}} = 3.24$). In the healthy group, the strength of iFC negatively correlated with CDI ($r = -0.5$, $n = 33$, $p = 0.005$), but positively correlated with BIS ($r = 0.38$, $n = 31$, $p = 0.049$), Fun ($r = 0.29$, $n = 31$, $p = 0.147$), and Reward ($r = 0.49$, $n = 31$, $p = 0.01$). A contrary pattern was found in the anxious group where the strength of iFC was positively correlated with CDI ($r = 0.164$, $n = 32$, $p = 0.405$) and negatively correlated with BIS ($r = -0.239$, $n = 29$, $p = 0.25$), Fun ($r = -0.238$, $n = 29$, $p = 0.252$), and Reward ($r = -0.338$, $n = 29$, $p = 0.098$).

3.3.2.3. By diagnostic group: In general, the anxiety group failed to reveal any significant behavior*iFC correlations. Regarding the healthy group, several behavioral correlates emerged. First, the CDI was significantly negatively correlated with the NAcc*Caudate iFC ($r = -0.50$, $n = 33$, $p = 0.005$). Second, BIS and BAS-Reward sub-scales were significantly positively correlated with the same cluster (BIS: $r = 0.38$, $n = 31$, $p = 0.049$; BAS-Reward: $r = 0.49$, $n = 31$, $p = 0.01$). Finally, DC*Insula iFC positively correlated with the SCARED Social Anxiety Disorder subscale ($r = 0.46$, $n = 34$, $p = 0.011$) (see Table 5). Three of the correlations found to be significant in the healthy group, i.e., NAcc*Caudate iFC with CDI, BIS and BAS-Reward subscales differed significantly from those in the anxious group, as described above in between-group comparisons (Table 4 and Table 5).

4. Discussion

This is the first study to compare striatal intrinsic functional connectivity (iFC) in adolescents with anxiety disorders to healthy adolescents. Findings are four-fold. First, as predicted, striatal iFC distinguished the anxious from the healthy group. Second, striatal iFC was lower in the anxious than healthy adolescents across all significant clusters. Third, striatal iFC group differences involved significant clusters within system (striatum-to-striatum) and between systems (striatum-to-PFC). Finally, as predicted, there were anxiety-associated connectivity differences with both ventral and dorsal striatal seeds.

Specifically, anxiety showed lower iFC of (1) left nucleus accumbens (NAcc) with right caudate, (2) right dorsal caudate (DC) with right subgenual anterior cingulate cortex (sgACC) and left posterior insula, and (3) left DC and right ventral caudate (VC) with

supplementary motor area (SMA). The following discussion will consider iFC of the nucleus accumbens (NAcc), dorsal caudate (DC) and ventral caudate (VC) seeds separately.

First, we address the connectivity between the left NAcc seed and the right caudate nucleus. This within-striatal network perturbation suggests abnormalities in the transmission of motivational information from the NAcc (Carelli, 2002; Jensen et al., 2007; Knutson et al., 2001) to the cognitive/motor part of the striatum, the caudate nucleus (Hikosaka, Kim, Yasuda, and Yamamoto, 2014). Although iFC does not provide information on the direction of information flow, this interpretation fits with models of ventral-dorsal striatal functional organization (Di Martino et al., 2008; Haber and Knutson, 2010; Hart et al., 2014). These models propose that the NAcc estimates the motivational values of stimuli, and the dorsal striatum translates these values into actions through information integration and transmission to effector regions in the prefrontal and motor cortex (Takahashi et al., 2008). The lower NAcc-Caudate iFC suggests poor translation of value to action in adolescent anxiety. In addition, the type of information most consistently associated with this path is appetitive (Carelli, 2002; Haber and Knutson, 2010; Jensen et al., 2007; Knutson et al., 2001). In support of this contention, our exploratory data show that the NAcc*caudate connectivity is correlated negatively with the severity of depressive symptoms (CDI) (e.g., the weaker the connection, the more severe the depressive symptoms) and correlated positively with sensitivity to reward (as measured by the BAS-reward subscale) in healthy subjects. Interestingly, this association with behavior was not significant in the anxious group, supporting the idea that the integration of positive valuation may be disrupted in clinical anxiety.

Second, the right DC seed showed lower iFC in anxious vs. healthy adolescents in two clusters, the sgACC and the posterior insula. According to the ventral-dorsal model of the striatum (Alexander et al., 1986; Parent and Hazrati, 1995), group differences in dorsal caudate connectivity suggest changes in the cognitive/motor fate of the information carried by these connections. Both the sgACC and posterior insula have been involved in the coding of emotions (Chang et al., 2013; Drevets et al., 2008; Gaffrey et al., 2010; Greicius et al., 2007; Horn et al., 2010), integration of visceromotor information (Chang et al., 2013; Craig, 2003, 2011; Freedman et al., 2000), and translation of representations into actions (Chang et al., 2013). In addition, the sgACC has been implicated in fear regulation, particularly fear extinction (Milad and Quirk, 2012; Phelps et al., 2004) and anxiety disorders such as PTSD (Keding and Herringa, 2015). In anxiety, Britton (Britton JC et al., 2013) found weaker activation of this region during threat appraisal. While most studies implicate the amygdala as the target of the sgACC dysfunction (Hartley and Phelps, 2010; Phelps et al., 2004), the present work suggests an additional target, i.e., the striatum, in adolescent anxiety.

Furthermore, the sgACC has also been extensively studied in the context of depression, and found to be a critical link to the expression of depressed mood (Drevets et al., 2008; Siegle et al., 2012). Due to the high comorbidity found between MDD and anxiety disorders (Beesdo et al., 2007; Costello et al., 2003; Stein et al., 2001), abnormal communication between the striatum and sgACC might represent a risk factor for the development of depression in anxiety disordered patients. In addition, given the role of sgACC in negative affect, this finding might reflect the abnormal processing of negative emotions in anxiety.

The abnormally low right DC*posterior insula iFC in the anxious group might reflect poor integration of cognitive/motor signals carried by the dorsal striatum (Alexander et al., 1986) with interoceptive stimuli that are processed in the posterior insula (Craig, 2002, 2003, 2011). In fact, misinterpretation of interoceptive stimuli was recently proposed to characterize anxious states (Paulus and Stein, 2010).

Finally, the right VC and right DC showed abnormally low iFC with SMA/BA6 regions in anxious participants. These regions contribute to movement preparation and other motor-related processes, such as motor inhibition or response switch (Nachev, Kennard, and Husain, 2008). Lower connectivity of this striatal*SMA/BA6 link in anxiety might reflect a disturbance of the translation of motivational goals into action due to impaired flow of information to motor effectors. Highly speculative, it might be a reflection of a bias towards avoidance, a hallmark of anxiety (Aupperle and Paulus, 2010; Giorgetta et al., 2012; Levita, Hoskin, and Champi, 2012; Lorian and Grisham, 2010; Maner and Schmidt, 2006).

Taken together, the present findings call for two general comments. First, the abnormally low striatal connectivity suggests poorer coordination of signaling within striatal regions, and between striatum and prefrontal regions in anxious compared to healthy adolescents. Based on the notion that the strength of functional connectivity might reflect the history of use, or the readiness-to-be-engaged of connections (Guerra-Carrillo et al. 2014), lower connectivity might suggest poor or disorganized integration of information across striatal connections. Second, anxiety-related striatal iFC did not involve the putamen seeds. This suggests that the putamen is less implicated in adolescent clinical anxiety than is the NAcc or caudate nucleus. However, several prior task-based fMRI studies demonstrated that the putamen function is compromised in clinically anxious adolescents (Guyer et al., 2012; Liu et al., 2015). Additionally, at least one resting state fMRI study in anxious adults (Manning et al., 2015) reported perturbed putamen connectivity. Taken together, it appears that more studies are needed to elucidate the role of the putamen in anxiety disorders in adolescents.

On further examination of the adult studies, the present findings exhibit similarities with and differences from the two neuroimaging works in adults with SAD (Arnold Anteraper et al., 2014; Manning et al., 2015). Similarly to these studies, we found altered connectivity within the striatum and between the striatum and prefrontal regions. However, the direction of the changes was not consistent. While we found abnormally low connectivity in anxiety for all clusters, Anteraper (Arnold Anteraper et al., 2014) found consistently higher striatal iFC in SAD vs. healthy adults, while Manning (Manning et al., 2015) described both higher and lower striatal iFC in SAD vs. healthy adults. Such discrepancy between our findings in adolescents and these previous findings in adults could be evidence of the evolution of striatal abnormalities with age, or it could also reflect the type of anxiety disorders under study. Our sample included heterogeneity of primary anxiety disorders (GAD, SAD, with high comorbidity among these disorders and specific phobia). Although we attempted to dissociate the effects of GAD and SAD (see supplemental material), the low number of participants in each group of single diagnosis (only GAD, only SAD) provided insufficient power to detect reliable differences, as addressed below in the limitation section.

The present findings should be interpreted with some limitations. First, the sample sizes were not large enough to examine the contributions of factors such as age, gender or IQ. However, to minimize the potential influence of these factors, both patient and healthy groups were carefully matched on sex, IQ, and age, and these factors were also controlled in the group analysis. Second, the acquisition scheme used for this study seemed to emphasize susceptibility artifacts in the right NAcc resulting in poor EPI coverage of this region. Twelve subjects had poor EPI coverage in the right NAcc area, while only three subjects had poor coverage in the left NAcc area. Of note, previous RSFC studies of striatal connectivity in adults (Di Martino, 2008) and children (Porter, 2015) did not find strong evidence for functional hemispheric lateralization in the NAcc connectivity. A third limitation was our inability to examine findings as a function of type of anxiety disorder, e.g., SAD vs. GAD. The anxiety group comprised patients with comorbid anxiety disorders, which is a typical presentation of clinical anxiety in adolescence (Beesdo et al., 2009; Copeland et al., 2013; Costello et al., 2003). Based on the visual inspection of the distribution of primary disorders across the significant striatal iFC clusters (Figs. 1–3), findings did not seem to differ among anxiety disorders. Accordingly, additional comparisons of the mean iFCs for the three largest diagnostic categories (GAD, SAD and GAD comorbid with SAD) failed to reveal statistically significant differences between anxiety diagnoses. Leveraging this diagnostic heterogeneity, the patient sample was homogeneous with regard to severity of anxiety symptoms and the absence of medication. Indeed, patients entered the study only if they were seeking treatment (inclusion criterion), and none of them were on medication or had started psychotherapy. Therefore, the present study might capture the neural correlates of a common dimension across anxiety disorders. This conclusion would need to be confirmed in larger samples of patients carrying non-comorbid diagnoses. The fourth limitation concerns the use of 4 different scanners. Several factors mitigate this limitation: (1) groups were matched on scanners, (2) scanners were of the same field strength (3T), design model (General Electric) and located at the same site, (3) the acquisition sequence was the same across scanners, and (4) scanner was used as a covariate in all group level GLMs. Finally, findings seem to show lateralization effects. Unfortunately, too little information is currently available in the literature on the functional significance or specificity of striatal functional lateralization to be able to discuss this effect.

In conclusion, abnormally low intrinsic functional connectivity of both dorsal and ventral striatal regions seems to characterize clinically anxious adolescents. Striatal iFC clusters involved regions that process motivational, emotional, interoceptive, and motor information, a pattern which is consistent with the multidimensional deficits characteristic of anxiety disorders. These dysfunctional striatal networks might contribute to the negative affect as well as behavioral avoidance proclivity (Aupperle and Paulus, 2010; Levita et al., 2012) and risk aversion (Giorgetta et al., 2012; Lorian and Grisham, 2010; Maner and Schmidt, 2006) described in this population. Connectivity studies are likely to become increasingly important to the clinical field. Indeed, therapeutic interventions at the level of brain circuitry might become feasible in the near future. Promising upcoming techniques such as online neuro-feedback (Hammond, 2005; Scheinost et al., 2013; Simkin, Thatcher, and Lubar, 2014; Stoeckel et al., 2014; Yuan et al., 2014), transcranial magnetic brain stimulation (Paes

et al., 2011; Pigot et al., 2008; Zwanzger et al., 2009), or behavioral interventions might be developed to strengthen frontal-striatal networks in anxiety disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.neuropsychologia.2016.03.019>.

Fig. 1.

Anxiety is associated with lower intrinsic functional connectivity (iFC) within striatum. (A) Decreased iFC between left NAcc seed and head and body of right Caudate (cluster size is 1593 μ l, $(F(1,69)=20.81; p=0.00002)$). (B) Scatterplot shows connectivity differences between healthy and anxious groups. Within anxious group, colors are used to highlight specific anxiety disorders and co-morbidity with major depressive disorder. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 2.

Anxiety is associated with lower iFC of striatum with regions of prefrontal cortex (e.g. right dorsal caudate (DC) with right subgenual anterior cingulate cortex (sgACC) and left posterior insula. (A) Decreased iFC between right Dorsal Caudate (DC) seed and left Posterior Insula (cluster size is 2646 μ l, ($F(1,69)=18.02$; $p=0.00008$). (B) Scatterplot shows connectivity differences between healthy and anxious groups. Within anxious group, colors are used to highlight specific anxiety disorders and co-morbidity with major depressive disorder. (C) Decreased iFC between right DC and right subgenual Anterior Cingulate Cortex (sgACC) (cluster size is 2025 μ l, ($F(1,69)=21.23$; $p=0.00002$). (D) Scatterplot of connectivity by diagnostic groups.

Fig. 3.

Anxiety is associated with lower iFC of striatum with supplementary motor area (SMA). (A) decreased connectivity between left Dorsal Caudate (DC) and left Middle Frontal Gyrus (cluster size is 2808 μ l, ($F(1,69)=15.14$; $p=0.0003$). (B) Scatterplot shows connectivity differences between healthy and anxious groups. Within anxious group, colors are used to highlight specific anxiety disorders and co-morbidity with major depressive disorder. (C) Decreased connectivity between right Ventral Caudate (VC) and right Superior Frontal Gyrus (cluster size is 1998 μ l, ($F(1,69)=19.93$; $p=0.00005$). (D) Scatterplot of connectivity by diagnostic groups.

Fig. 4.

Behavioral correlates of group differences in iFC. Healthy and Anxious groups differed significantly in correlations between DC*posterior insula iFC and SCAREDpc-GAD ($z_{\text{obs}} = 2.28$). DC*posterior insula iFC positively correlated with GAD severity as measured by SCAREDpc-GAD for healthy group ($r = 0.261$, $n = 34$, $p = 0.163$), but negatively correlated with GAD severity for anxious group ($r = -0.303$, $n = 34$, $p = 0.104$).

Table 1

Study demographic and diagnostic characteristics.

Variables:	Anxious n=35	Healthy n=36
Mean Age (SD)	13.2 (2.7)	13.0 (2.7)
Female n (%)	21 (60%)	21 (58%)
Mean IQ (SD)	110.2 (14.7)	111.3 (11)
Mean SES (SD)	38.7 (20.6)	40.9 (21)
Mean maximum displacement (SD)	1.3 (0.8)	1.4 (0.8)
Mean % TR censored (SD)	0.04 (0.05)	0.04 (0.05)
Subjects excluded due to motion n (%)	31 (44%)	30 (34%)
Mean SCARED-pc (SD) *	32.7 (10.7)	6.4 (5.2)
Mean CDI (SD) **	11.9 (7.1)	2.1 (2.2)
Mean FNE (SD) ***	18.2 (9.2)	5.9 (4.3)
Mean BIS (SD)	22.6 (4.4)	17.9 (3.8)
Mean BAS Fun (SD)	11.5 (2.1)	12.2 (1.9)
Mean BAS Reward (SD)	16.5 (2.0)	17.4 (1.7)
Mean BAS Drive (SD)	9.9 (2.7)	10.6 (2.4)
Mean BIS-BAS (SD)	37.8 (5.9)	40.4 (4.5)
Anxiety diagnoses:		
GAD	11	0
SAD	8	0
GAD and SAD	16	0
Specific phobia	6	0
Separation Anxiety	7	0
Other diagnoses:		
MDD	2	0
ADHD	1	0
ODD	1	0

Anxious and healthy groups differed on the measures of anxiety (SCARED-pc), depression (CDI), and social anxiety (FNE).

GAD= Generalized Anxiety Disorder.

SAD=Social Anxiety Disorder.

MDD=Major Depressive Disorder.

ADHD=Attention Deficit Hyperactivity Disorder.

ODD=Oppositional Defiant Disorder.

SCARED-pc= Screen for Anxiety Related Disorders (SCARED) average of the child and parent responses.

CDI= Children's Depression Inventory.

FNE= Fear of Negative Evaluation.

BIS= Behavioral Inhibition System.

BAS= Behavioral Approach System.

* SCARED-pc ($t = -13.11$, ($p = 1.14\text{E-}17$, $df = 49$)),

** CDI ($t = -7.66$, ($p = 7.4\text{E-}9$, $df = 37$)), and

*** FNE ($t = -6.77$, ($p = 2.3\text{E-}8$, $df = 45$))

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Table 2

Significant group differences.

Seed	Cluster peak	Cluster size (μl)	F (1,69)	p	X	Y	Z	Healthy (z-average)	Anxious (z-average)
L NAcc	R Caudate	1593	20.81	0.00002	13.5	1.5	14.5	0.1	-0.03
R DC	L Posterior Insula	2646	18.02	0.00008	-43.5	-25.5	11.5	0.17	0.03
R DC	R sgACC	2025	21.23	0.00002	7.5	25.5	-0.5	0.17	0.04
L DC	L MFG (SMA)	2808	15.14	0.0003	-4.5	-16.5	59.5	0.09	-0.03
R VC	R SFG (SMA)	1998	19.93	0.00005	16.5	22.5	53.5	0.11	-0.01

(X, Y, Z) are reported in Talairach Coordinates.

L=left, R=right.

sgACC= Subgenual anterior cingulate cortex.

SMA= Supplementary motor area.

MFG= Middle frontal gyrus.

SFG= Superior frontal gyrus.

Table 3

Whole sample behavioral correlates.

	SCARED _{pc}	CDI	FNE
R VC to SMA	$r = -0.39, p = 0.004$	$r = -0.34, p = 0.011$	$r = -0.4, p = 0.003$
R DC to L posterior insula	$r = -0.46, p < 0.005$	$r = -0.43, p = 0.001$	$r = -0.36, p = 0.007$
R DC to R sgACC	$r = -0.38, p = 0.005$	$r = -0.4, p = 0.003$	$r = -0.45, p = 0.001$
L DC to SMA	$r = -0.4, p = 0.003$	$r = -0.33, p = 0.015$	$r = -0.29, p = 0.032$
L NAcc to R Caudate	$r = -0.45, p = 0.001$	$r = -0.36, p = 0.007$	$r = -0.45, p = 0.001$

df=53

Table 4

Significant anxious vs. healthy group comparisons.

Connectivity	Behavior	Healthy	Anxious	Zobs
DC*Insula	SCAREDpc_GAD	$r=0.26$, $n=34$, $p=0.163$	$r=-0.30$, $n=34$, $p=0.104$	2.28
NAcc*Caudate	CDI	$r=-0.5$, $n=33$, $p=0.005^*$	$r=0.164$, $n=32$, $p=0.405$	-2.75
NAcc*Caudate	BIS	$r=0.38$, $n=31$, $p=0.049^*$	$r=-0.239$, $n=29$, $p=0.25$	2.37
NAcc*Caudate	BAS Fun	$r=0.29$, $n=31$, $p=0.147$	$r=-0.238$, $n=29$, $p=0.252$	1.97
NAcc*Caudate	BAS Reward	$r=0.49$, $n=31$, $p=0.01^*$	$r=-0.338$, $n=29$, $p=0.098$	3.24

Table 5

Significant connectivity vs. behavioral measures correlations in healthy group.

Connectivity	Behavior	Correlations
DC*Insula	SCAREDpc_SAD	$r=0.46$, $n=34$, $p=0.011$
NAcc*Caudate	CDI	$r=-0.5$, $n=33$, $p=0.005$
NAcc*Caudate	BIS	$r=0.38$, $n=31$, $p=0.049$
NAcc*Caudate	BAS Reward	$r=0.49$, $n=31$, $p=0.01$