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Reduced insular volume in attention deficit hyperactivity disorder

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Abstract

The aim of this study was to evaluate whether structural differences in the insula and anterior cingulate (ACC), two critical areas of the "salience network," co-exist in adolescents with ADHD compared to healthy controls (HC). In addition we aimed to determine if structural changes within these regions correlate with attention and inhibitory function. Nineteen adolescents with ADHD and 25 HC received MRI scans on a 3T magnet. Morphometric analysis was performed with FreeSurfer. Youths with ADHD were found to have a bilateral reduction in anterior insular (AIC) gray matter volumes compared to HC. Furthermore, the left AIC was found to positively correlate with oppositional symptoms, while the right AIC was found to associate with both attention problems and inhibition. To our knowledge this is the first report of a bilateral reduction in AIC volumes in ADHD. Our findings suggest a role for the insula in modulating attention and inhibitory capacity in ADHD.

Keywords

ADHD; Adolescents; Imaging; Cortical Thickness; Insula

1. Introduction

Inattention, impulsivity and hyperactivity are the core symptoms of Attention-Deficit Hyperactivity Disorder (ADHD) (American Psychiatric Association, 2000a). The anterior cingulate cortex (ACC) has been shown to play a critical role in attention, emotion and cognitive processing and the integrity of this region has been extensively evaluated in youths with ADHD (Adler et al., 2005, Bush et al., 2000, Makris et al., 2007, Narr et al., 2009, Shaw et al., 2006). Morphometrically, reduced cortical thickness in the ACC has been

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reported both in children and adults with ADHD (Makris et al., 2007, Narr et al., 2009, Seidman et al., 2011, Seidman et al., 2006, Shaw et al., 2006). Task-based functional MRI studies in ADHD have reported atypical activation patterns, primarily hypoactivation, in the ACC on a variety of attention and executive functioning tasks (Bush et al., 1999, Ernst et al., 2003, Konrad et al., 2006, Smith et al., 2008). Finally, studies examining functional connectivity in youths with ADHD have reported abnormal functional connections of the ACC to other brain regions, including the insula (Tian et al., 2006, Zang et al., 2007). These findings in combination with the hypothesized role of the ACC in attention and cognition suggest that the ACC is a central brain structure involved in the pathophysiology of ADHD.

Interestingly, the ACC and insula have been found to co-activate on numerous functional imaging studies including those involved in goal-directed attention and emotion and both are crucial structures in the salience network (Craig, 2009, Medford and Critchley, 2010, Menon and Uddin, 2010). The salience network has been proposed to detect and segregate incoming internal and external stimuli and provides this information to other brain regions in order to guide appropriate behavioral responses to that stimuli and includes the bilateral anterior insula (AIC) and ACC (Menon and Uddin, 2010, Seeley et al., 2007, Sridharan et al., 2008). The proposed role of the AIC in the salience network is in the detection and segregation of important from insignificant stimuli, while the ACC modulates responses in the sensory, motor and association cortices based on the information provided by the AIC (Menon and Uddin, 2010). Furthermore, the salience network may engage in the recruitment of the appropriate brain regions for the processing of current stimuli and the down regulation of formerly engaged networks (Palaniyappan and Liddle, 2012). The right AIC, has been proposed to play a critical role in switching between 2 major brain networks, the default mode network (DMN), and the central executive network, which have competitive interactions during cognitive information processing (Sridharan et al., 2008). The insula has also been associated with attention, decision-making, cognitive control, performance monitoring, body movement, emotional awareness, risk uncertainty and anticipation (Craig, 2009). Despite the wide array of cognitive functions associated with the insula, few studies to date have evaluated the morphology of the insula in ADHD, and the reports thus far, have been negative (Filipek et al., 1997, Hynd et al., 1993). For instance, Hynd and colleagues examined the length of the right and left insula in 10 youths with ADHD and did not find a significant difference compared to 10 age-matched controls (1993). A subsequent study by Filipek and colleagues did not find differences in left or right total insular volumes when they compared 15 healthy control (HC) youths and 15 youths with ADHD (1997).

More recently advanced imaging techniques have found insular abnormalities in several neuropsychiatric illnesses. For example, in a voxel-based morphometry analysis, Sterzer and colleagues found reductions in bilateral insular gray matter volumes in youths with conduct disorder (CD) compared to HC. Furthermore, a study of children with Smith-Magenis syndrome, which is associated with aggression, hyperactivity, and attention deficits also noted bilateral anterior insular gray matter reductions (Boddaert et al., 2004). Reductions in insular volumes have also been reported in other neuropsychiatric disorders including pervasive developmental disorder (Kosaka et al., 2010), bipolar disorder (Ellison-Wright and Bullmore, 2010) and schizophrenia (Ellison-Wright and Bullmore, 2010, Makris et al., 2006), suggesting that insular abnormalities are not specific to ADHD and may represent a

common neurodevelopmental biological marker of attentional and inhibitory function across disorders. In addition, increased anterior insula activity has been reported during risky decision-making tasks in HC (Lee et al., 2008, Paulus et al., 2003). In an fMRI study utilizing a task-switching paradigm, adults with ADHD had greater activation in the dACC and insula, while controls displayed more activation in brain regions, which included DMN regions (Dibbets et al., 2010). Furthermore, a recent study by Tian and colleagues comparing the resting-state dACC functional connectivity patterns in adolescents with and without ADHD, found that ADHD patients had stronger connections with the bilateral dACC and bilateral insula, as compared to HC (2006).

Given that the ACC and insula have been found to co-activate on numerous functional imaging studies and that the connectivity of the ACC and insula has been shown to be different in ADHD, structural investigations of the insula and ACC, two critical areas of the "salience network," is warranted in ADHD. Both ACC subregions were included in the "salience network" as the rostral or "affective" ACC subregion has been linked to the assessment of the salience of emotional and motivational information while the caudal ACC or "cognitive" region has been found to mediate attention and executive functions (Bush et al., 2000, Laurens et al., 2003, Margulies et al., 2007). Therefore, the aim of this study was to evaluate whether gray matter volumes in the anterior and posterior insula and rostral and caudal ACC were different between adolescents with ADHD compared to healthy controls (HC). The Child Behavior Checklist (CBCL) has been utilized frequently to assess internalizing and externalizing symptoms in children with psychiatric illnesses (Achenbach and Rescorla, 2001). The Conner's Parent Rating Scale – Revised – Long Version (CPRS) (Conners, 2008) and the Continuous Performance Test (CPT) (Conners, 2000), were utilized to assess attention and impulsivity. We predicted that gray matter volumetric reductions would be present in the ACC and AIC in youths with ADHD and that these reductions would correlate with measures of attention and impulsivity.

2. Methods

2.1. Subjects

The Institutional Review Board at the University of Utah approved this study. All subjects were recruited from the community via local advertisements and word of mouth advertizing. Study subjects were age 10–18 years old, male or female, right-handed, of any race or ethnicity. Inclusion criteria for ADHD subjects included a DSM-IV-TR diagnosis of ADHD, inattentive or combined type. All psychiatric diagnoses, including drug and alcohol dependence were based on a clinical and diagnostic semi-structured interview (Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Episode (K-SADS-PL) (Kaufman et al., 1997) by a board-certified child psychiatrist (MLL). A clinical meeting to review all participants in this study was performed and all diagnoses were confirmed during this meeting via clinician consensus (DYT, MLL, ECM). In addition, parents of participants were asked about past and current active medical and neurological disorders and family histories of psychiatric disorders. Healthy control participants had no current or past history of a DSM-IV-TR Axis I diagnosis based on structured and clinical interviews. Exclusion criteria for all subjects included: major

sensorimotor handicaps (e.g., deafness, blindness, paralysis); full scale IQ < 70; history of claustrophobia, autism, schizophrenia, anorexia nervosa or bulimia, drug or alcohol dependence; active medical or neurological disease; metal fragments or implants; and current pregnancy or lactation. All adolescents provided written assent to participate in the study, and their parents (or legal guardians) provided written informed consent.

A total of 22 youths with ADHD and 26 HC were recruited for the study. Three of the 22 youths with ADHD had significant motion abnormalities detected on MRI processing and were excluded from the study. In addition, one HC participant was noted to have a significant structural abnormality and was excluded from the study. Therefore, nineteen adolescents with ADHD were included in this analysis (ADHD, 10 males, 9 females, mean age 14.00 ± 2.43; 84.21% Caucasian), along with 25 age matched healthy control participants (HC, 12 male, 13 female, mean age 14.28 ± 2.73; 92.00% Caucasian). (See Table 1 for demographic and clinical information). The DSM-IV-TR Global Assessment of Functioning was used to assess global functioning (American Psychiatric Association, 2000b). Participants' parents were asked to complete the CBCL and CPRS, and all participants were asked to perform the CPT. All data were converted to *t*-scores prior to additional analyses. The Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) was administered to obtain full-scale intelligence quotients on participants (FSIQ).

2.2. Magnetic resonance imaging

Structural imaging was performed at the Utah Center for Advanced Imaging Research (UCAIR) using a 3T Siemens Trio scanner. Structural acquisitions include a T1-weighted 3D MPRAGE grappa sequence acquired sagittally, with TE/TR/TI=3.38ms/2.0s/1.1s, 8° flip, 256x256 acquisition matrix, 256 mm^2 FOV, 160 slices, 1.0 mm slice thickness. The original imaging data were transferred from the scanner in the DICOM format and anonymized. On first subject specific level analysis, each of the subjects' cortical thickness was estimated within the FreeSurfer image analysis environment (http://surfer.nmr.mgh.harvard.edu/) (Dale et al., 1999, Fischl et al., 1999a, Fischl et al., 1999b). First the high resolution T1 MPRAGE volumes were converted to FreeSurfer's specific format, normalized for intensity and resampled to isotropic voxels of 1 × 1 × 1 mm. Next, the skull was removed from the images using a skull-stripping algorithm (Segonne et al., 2004) and segmented into tissue types. The segmented white matter (WM) volume was used to derive a tessellated surface representing the gray–white boundary. The surface was automatically corrected for topology defects, and expanded to model the pial–gray boundary to produce a second, linked mesh surface. The distance between the gray–white matter boundary and the pial mesh was used to estimate cortical thickness. Individual subject's cortical thickness were normalized to the spherical-space standard curvature template with a number of deformable procedures including surface inflation and spherical registration that utilized individual cortical folding patterns to match cortical geometry across subjects. The cortex was partitioned using an automated Bayesian segmentation procedure designed to replicate the neuroanatomical parcellation defined by Destrieux and colleagues to produce gyral and sulcal cortical thickness and volumetric measures (Destrieux et al., 2010). Quality control was performed by a trained operator (JBK) throughout MRI processing within the FreeSurfer environment via manual visual inspection of each subjects' output to ensure

proper Talairach registration, skull stripping, cortical surface reconstruction, and subcortical segmentation to ensure output integrity.

The Destrieux parcellation data included 2 gyral and 4 sulcal output data for the insula (Destrieux et al., 2010). Both gyral and sulcal data are important when considering tissue volumes as a large proportion of volume lies within the sulcal folds. In attempts to capture this data, reduce the number of multiple comparisons, and make separate volumes for anterior and posterior insula regions, the authors combined the gyral and sulcal output into anterior and posterior insula regions based on anatomical location of the structures (Destrieux et al., 2010, Duvernoy and Bourgouin, 1999). Three regions were utilized to define the anterior insula and 3 regions were chosen to define the posterior insula as follows: the anterior insula included the insular short, the central insula sulcus and the sulcal circular insula anterior (See Figure 1). The posterior insula was defined as the sulcal circular insula superior, the sulcal circular insula inferior, and the gyral insular long. These insula subregions were obtained from the Destrieux 2005 atlas and include both gyral and sulcal measurements. The central sulcus of the insula runs antero-inferiorly from the superior segment of the circular segment of the insula and divides the insula in two parts: the short insular gyri (anterior) and the long insular gyrus (posterior). The central sulcus was included in the anterior insula. The other major insula sulcus is the circular sulcus of the insula and is divided into 3 segments including the superior, anterior and inferior. The anterior insula sulci limits the insula anteriorly from the orbital gyri and has been included in the anterior insula volume. The superior and inferior segment of the circular sulcus of the insula merge posteriorly and separates anterior/posterior insula from the inferior frontal gyri, and the superior temporal gyrus, respectively, and have been added to the insular long gyrus to make up the posterior insula. The decision to include the superior segment of the circular sulcus in the posterior insular subregion was based on the anteroventral and posteriodorsal cytoarchitectonic zones that approximate the connectivity-based insula subregions as described by Mesulam and Mufson and applied to human populations by Cohen and colleagues (Cohen et al., 2010, Mesulam and Mufson, 1982). For ACC, the right and left rostral and caudal ACC values were extracted as is and utilized for further analysis using the Desikan-Killiany atlas (Desikan et al., 2006).

IBM SPSS Version 19 for Macintosh (SPSS, Inc., Chicago, IL) was used for statistical analysis. All statistical tests were two-tailed with 3 = 0.05. Equality of groups on demographic and clinical variables was evaluated by Pearson's t-tests for continuous variables and chi-square tests for categorical variables. All regional brain volumes were first adjusted by total segmented brain volume (TBV) (structure/TBV *1000) prior to analyses. A MANOVA was performed to assess key regions of the "salience network," which included the right and left anterior and posterior insula and the right and left rostral and caudal ACC volumes entered as dependent variables, group and gender were independent variables and age was included as a covariate. The Wilks' Lambda was reported for each MANOVA and subsequent individual univariate statistics were reported for all brain regions that were significant after Bonferroni Correction (3/n). Therefore, structures were considered significant at a $P = 0.01$ given there were 8 structures within the MANOVA, and an 3 = 0.05. To assess whether or not insular subregions were significantly different between

youths with ADHD and HC, post-hoc analyses of individual insular subregions were performed and were considered significant at a $P = 0.01$ level. Pearson's correlations were performed with clinical measures of attention and impulsivity on the CBCL, CPRS and CPT for those brain regions that differed significantly between youths with ADHD and HC.

3. Results

3.1. Subjects

Nineteen adolescents with ADHD are included in this analysis along with 25 HC (See Table 1 for Demographic and Clinical Characteristics). Participants in the ADHD group were diagnosed with either ADHD combined type (63.16%) or inattentive type (36.84%) with 63.16% of the ADHD sample having a familial history of ADHD. Five of the ADHD participants (26.32%) carried one or more past or current comorbid diagnosis (history of depression ($n = 2$), past cannabis abuse ($n = 2$), current oppositional defiant disorder ($n = 2$), current mood disorder not otherwise specified ($n = 1$). Of the 19 ADHD study participants, 63.16% (n=12) were currently taking stimulant medications; of the 36.84% ($n = 6$) who were not, 71.43% of those individuals had a history of stimulant pharmacotherapy in the past. Four ADHD participants (21.10%) were currently taking one or 2 prescription medications other than stimulants, including (fluoxetine ($n = 1$), depakote ($n = 1$), imipramine ($n = 1$), trazodone ($n = 1$), zoloft ($n = 1$), and clonazepam ($n = 1$)).

Based on the CBCL, internalizing and externalizing symptoms were found to be higher in ADHD youth as compared to HC (both $P < 0.001$). Subscale *t*-scores of the CBCL assessing attention and rule-breaking behaviors were also found to be higher in the ADHD group (both $P < 0.001$). Additionally, CPRS subscale *t*-scores assessing oppositional behavior, cognitive problems, hyperactivity, and inattentive/impulsive behaviors were also significantly different between youths with ADHD and HC (all $P <0.001$). However, no significant between group differences were found for CPT measures. Healthy youths had higher GAF scores and FSIQ scores than youths with ADHD ($P < 0.001$ and $P < 0.01$, respectively) (see Table 1 for a details of clinical characteristics).

3.2. Anterior Cingulate and Insular Volumes

An initial MANOVA was performed which included the right and left anterior and posterior insula and right and left rostral and caudal ACC volumes as dependent variables, group and gender as independent variables and age as a covariate. In this initial model the effect of age was not found to be significant (Wilks' Lambda = 0.92, $F(8,32) = 0.33$, $P = 0.95$) and was excluded from further analyses. After excluding age, there was a significant effect for group, at a trend level (Wilks' Lambda = 0.67, $F(8,33) = 2.06$, $P = 0.07$), and gender (Wilks' Lambda = 0.65, $F(8,33) = 2.26$, $P = 0.05$). Youths with ADHD had significantly smaller right ($F(1,40) = 8.77$, $P = 0.01$) and left ($F(1,40) = 8.09$, $P = 0.01$) anterior insula regions compared to HC (See Table 2 and Figure 2). The posterior insula and the right and left ACC subregions were not found to be significantly different between youths with ADHD and HC. Both the left posterior insula ($F(1,40) = 9.71$, $P < 0.01$) and left caudal ACC ($F(1,40) = 7.64$, $P = 0.01$) were found to be smaller in males as compared to females. There was no significant sex by diagnosis interaction found. Post-hoc univariate analyses of left and right

anterior insula subregions found that the right insular short ($F(1,42) = 7.22$, $P = 0.01$), the left central insula ($F(1,42) = 7.60$, $P = 0.01$), and the left circular anterior insula ($F(1,42) = 14.52$, $P < 0.001$) subregions were driving the results of the study. Although the composite posterior right and left insular regions were not significant between groups, individual subregions such as the right insular long ($F(1,42) = 5.4$, $P = 0.03$) and left circular superior insula ($F(1,42) = 3.15$, $P < 0.08$) trended toward being smaller in the ADHD group compared to HC (See Table 2).

When we reanalyze the salient network excluding sulcal measurements and utilizing gyral insula short for the anterior insula and gyral insular long for the posterior insula, again the overall MANOVA was significant for group (Wilks' Lamda = 0.73, $F(39,4) = 3.9$, $P = 0.01$). Follow-up univariate analyses from this model found significant group differences for the right insula short gyrus (anterior insula) ($F(1,42) = 7.22$, $P = 0.01$) and a trend for the right insula long gryus (posterior insula) ($F(1,42) = 5.4$, $P = 0.03$) after Bonferroni correction. The left anterior insula was not found to be significant between groups.

3.5. Correlations with Conner's Parent Rating Scale, the Child Behavioral Check List and Continuous Performance

Test Both the composite left and right AIC volumes were found to be significant and were selected for additional correlational analyses with attention and impulsivity measures from the CPRS, CBCL and the CPT. In ADHD youths, the left AIC volumes were significantly correlated with the CPRS Oppositional subscale *t*-score ($r(18) = 0.47$, $P = 0.05$) and CBCL rule-breaking behavior subscale *t*-score ($r(18) = 0.61$, P = 0.01), while the right AIC adjusted volumes were significantly correlated with the CBCL attention problems subscale *t*-score ($r(18) = 0.50$, $P = 0.03$). In the ADHD group, right AIC volumes were found to negatively correlate with CPT commission *t*-scores ($r(18) = -0.49$, $P = 0.03$).

3.6 Correlation with Medication and FSIQ

Neither duration of stimulant exposure, current dose of stimulant medication (mg/kg), or FSIQ was correlated with either left or right AIC subregions. Furthermore, FSIQ also did not correlate with either AIC region.

4. Discussion

To our knowledge, this is the first report of reduced bilateral AIC volumes, particularly the right AIC, in youths with ADHD. In ADHD youths, left AIC volumes were positively correlated with oppositional scores for both the CPRS and CBCL, while the right AIC adjusted volumes were positively correlated with the CBCL attention problems subscale score. In addition, the right AIC volumes were found to negatively correlate with CPT commission *t*-scores in the ADHD group. Our findings are in contrast to the 2 previous studies that looked specifically at insular morphometry and found no differences in youths with ADHD (Filipek et al., 1997, Hynd et al., 1993). There are a number of potential reasons for the discrepant results including differences in methodology, clinical population and rates of comorbidity. For example, Hynd and colleagues measured the length of the right and left insula on one 7.5mm thick sagittal slice obtained from a 0.6 Tesla magnet in a sample of 2

girls and 8 boys per group with high comorbidity rates (70%) and average IQs of 109 (1993). Filipek and colleagues had an all male population and utilized a 1.5 Tesla scanner with 3mm thick slices to evaluate total right and left insula in a sample of all boys with no comorbidities and higher IQs (average = 120) (1997). In contrast this current study utilized a 3.0 Tesla magnet with 1mm slice thickness and separately analyzed anterior and posterior insula volumes. Our sample population was equally mixed with males and females with a comorbidity rate of 26% and the FSIQ in our ADHD sample was 106. As this is a cross-sectional study and insular development has been described as linear for the AIC and quadratic for the body of the insula over the first few decades of life with peak cortical thickness occurring at the age of 18 (Shaw et al., 2008), the cause of the reduction in bilateral anterior insular volumes is unclear. Developmental delay in brain maturation has been previously described in ADHD (Castellanos et al., 2002, McAlonan et al., 2007, Shaw et al., 2007), suggesting insular volumes may normalize later in life; however, persistently smaller insular volumes into adulthood, related to aberrant insular maturation, cannot be ruled out.

Interestingly, reductions in insular volumes have been reported in other neuropsychiatric disorders including pervasive developmental disorder (Kosaka et al., 2010), bipolar disorder (Ellison-Wright and Bullmore, 2010) schizophrenia (Ellison-Wright and Bullmore, 2010, Makris et al., 2006), conduct disorder (CD) (Sterzer et al., 2007) and Tourette's Syndrome (Fahim et al., 2009). For example, Sterzer and colleagues found reductions in bilateral insular gray matter volumes in youths with CD compared to HC (Sterzer et al., 2007). In a study of children with Smith-Magenis syndrome, reduced bilateral anterior insular gray matter reductions (Boddaert et al., 2004) were also found. In a recent study of fraternal twins concordant for Tourette syndrome, cortical thickness in ACC and insula was found to be highly heritable in siblings as measured by a high intra-class correlation coefficient. Thickness of the right insula was negatively correlated with tic severity suggesting that insular morphometry is genetically driven and that structural changes may be associated with impaired inhibition (Fahim et al., 2009). Furthermore, there is extensive evidence indicating a role for the insular cortex in abstinence and relapse to drug seeking behavior and irregularities in insular thickness and density have been associated with drug abuse (Franklin et al., 2002, Makris et al., 2008, Schwartz et al., 2010). Moreover, adolescent cannabis abusers have been shown to have altered cortical thickness (Lopez-Larson et al., 2011) and adolescent males with antisocial substance abuse disorder tested in a risky decision task showed decreased insula activation when contrasted with HC (Crowley et al., 2010). Taken together these findings suggest that insular abnormalities are not specific to ADHD but rather may represent a common neurodevelopmental biological marker of attentional and inhibitory function across psychiatric and substance abuse disorders.

Our findings also differed from results of earlier morphometric studies in that we did not find reduced rostral or caudal ACC volumes in youths with ADHD. This may be due to a number of methodological differences between studies including sample size, gender differences, clinical outcomes, morphometric measures, or scanner strength. For example, using a 1.5T magnet, Shaw and colleagues investigated global cortical thinning in a longitudinal study comprised of 163 youths with ADHD and 166 HC and reported reduced cortical thickness bilaterally within the medial prefrontal and cingulate cortex in a subset of

ADHD subjects identified as having a worse clinical outcome (2006). In another study investigating cortical thickness differences between ADHD and HC youth, Narr and colleagues, reported widespread cortical thinning, including thinning of the ACC, in children and adolescents with ADHD in a primarily male population using a 1.5T magnet (2009). Furthermore, the 2 studies by Makris and colleagues (2007) and Siedman and colleagues (2006) investigated ACC morphometry in adults with a 1.5T magnet and reported significant differences within the cingulate cortex. In contrast the current study examined rostral and caudal ACC gray matter volumes using a 3.0T magnet in a group of adolescents that included an equal number of male and female subjects. Our cohort also contained ADHD youth with both combined and inattentive types.

Our data indicated that left AIC volumes were positively correlated with oppositional scores for both the CPRS and CBCL, while the right AIC was positively correlated with the CBCL attention problems in the ADHD group. In addition, the right AIC volumes were found to negatively correlate with CPT commission *t*-scores in the ADHD group. Few studies to date have evaluated behavioral measures of inhibition, aggression and impulsivity in association with insula volumes in psychiatric conditions. In one study, Sterzner and colleagues reported negative correlations between right insular volumes and measures of aggression on the CBCL in youths with CD (2007). This is in contrast to our finding of a positive correlation in the left AIC for oppositional symptoms in ADHD. Oppositional (rule-breaking behavior) and aggression are separate subscale scores on the CBCL and likely represent distinct behavioral markers of risk taking behaviors and sociopathy, respectively. For the present study, there were not enough youths in the ADHD cohort with significant aggressive symptomatology to make a direct comparison to the study performed by Sterzner and colleagues. The finding that oppositional behavior is increased with larger left AIC suggest a potential lateralization effect or maturational abnormality within the left insula. For example, on subregion analysis of the left insula, the insula short gyri, which is the main anterior insular region, is not significantly different in youths with ADHD compared to HC. The main regional abnormalities identified in the left AIC include the circular anterior insula sulci which separates the AIC from the orbital frontal gyri, and the central insula sulcus. This is in striking contrast to the right AIC insular short gyri, which is the main driver of the finding of right insular AIC abnormalities in ADHD.

Furthermore, the right AIC volumes were found to negatively correlate with CPT commission *t*-scores in the ADHD group suggesting that smaller right AIC volumes are associated with increased impulsivity. The right AIC was also positively correlated with CBCL attentional problems in the ADHD group, which suggest that increased attentional problems are also associated with larger AIC volumes. Correlational analyses of behavioral data within all the subregions of the right and left insula is beyond the scope of this manuscript given the small sample sizes; however, with much larger sample sizes, subregion and network analyses with behavioral data would be an important next step in assessing inhibitory and attentional domains within the salience network.

The insula and ACC are major hubs of the salience network and both have been found to co-activate on numerous functional imaging studies including those studying goal-directed attention and emotion (Anderson et al., 2011, Craig, 2009, Menon and Uddin, 2010). Once a

strong salient stimulus is detected by the AIC, it engages the ACC to mediate attention, working memory and higher order cognitive processes to respond to the salient stimuli, while at the same time the AIC disengages the DMN (Menon and Uddin, 2010, Sridharan et al., 2008). Furthermore, Palaniyappan et al., suggests the salience network is engaged in recruitment of the appropriate brain regions for the processing of current stimuli and the down regulation of formerly engaged networks (Palaniyappan and Liddle, 2012). Anterior insular hyperactivity has been reported in anxiety (Paulus and Stein, 2006, Stein et al., 2007) suggesting that the AIC may overestimate the emotional salience to ordinary events (Menon and Uddin, 2010). In addition, AIC hypoactivity has been reported in autism and may relate to the undervaluation of external social stimuli (Di Martino et al., 2009). Youths with ADHD are often easily distracted by mundane stimuli, suggesting a misattribution of salience, which may then lead to inappropriate signaling to the ACC and possibly erroneous engagement/disengagement of DMN and central executive networks potentially leading to the core ADHD symptoms of inattention, impulsivity and hyperactivity. Interestingly, failure to suppress DMN activity during task-related activities has been consistently reported in ADHD (Castellanos et al., 2008, Helps et al., 2010, Peterson et al., 2009, Qiu et al., 2011, Uddin et al., 2008). In addition, in an FMRI study utilizing a task-switching paradigm, adults with ADHD had greater activation in the dACC and insula, while controls displayed more activation in brain regions, which included DMN regions (Dibbets et al., 2010). Furthermore, a recent study by Tian and colleagues comparing the resting-state dACC functional connectivity patterns in adolescents with and without ADHD, found that ADHD patients had stronger connections with the bilateral dACC and bilateral insula, as compared to HC (2006).

Our current findings should be interpreted with care given the modest sample size, and cross-sectional nature of the study. Furthermore, the inclusion of youths with past and current comorbidities and stimulant medication use are also potential limitations of the study. However, all participants were off of their stimulant medication for at least 24 hours prior to scanning. Given the large number of youths on psychostimulants (63.2%), a subgroup analysis to look at the impact of medication in our results was not feasible. In addition, we have youths with ADHD with both combined and inattentive subtypes, which may have impacted our findings; again, however, due to the small sample size a subgroup analysis was prohibitive. Although we did not find any significant correlations between duration of stimulant use or current dose of stimulants, the effects of psychotropic medications, such as stimulants, on brain morphometry remain unknown. However, a study by Castellanos and colleagues found no differences in gray matter or TBV in medicated (stimulants) versus un-medicated youths and they found greater white matter deficits in unmedicated ADHD youths than in medicated youths with ADHD (2002), suggesting stimulants do not negatively affect brain morphometry. A number of studies have suggested suggest stimulant medications may diminish functional abnormalities (Epstein et al., 2007, Konrad et al., 2007, Stoy et al., 2011). For example, a study of adult males with ADHD revealed decreased functional activation in the insula when compared to those treated with methylphenidate and HC (Stoy et al., 2011). Additional analyses of ADHD youths with past or current comorbid diagnosis was also prohibitive given the range of diagnoses.

To our knowledge this is the first report of a bilateral reduction in anterior insular volumes in youths with ADHD. These reductions in anterior insular volumes were correlated with measures of inattention, impulsivity and oppositionality in youths with ADHD suggesting a role for the insula in modulating attention and impulsivity. Although we did not find ACC structural abnormalities in our youths with ADHD, our findings provide evidence that abnormalities within critical regions of the "salience network" exist in ADHD. Therefore, further evaluation of the "salience network" in ADHD is warranted.

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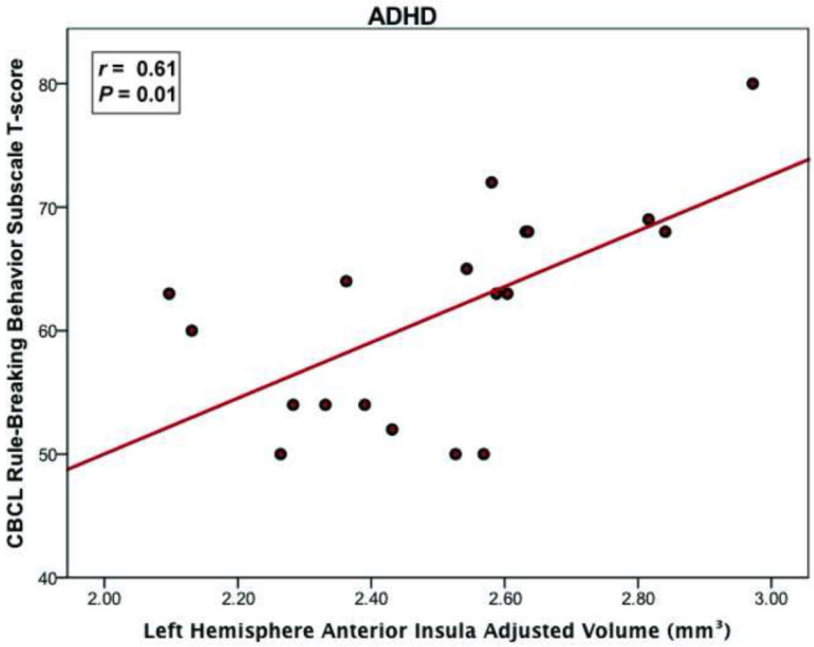

Figure 1.

Cortical Parcellation for the A) Insula and B) Anterior Cingulate Regions of Interest

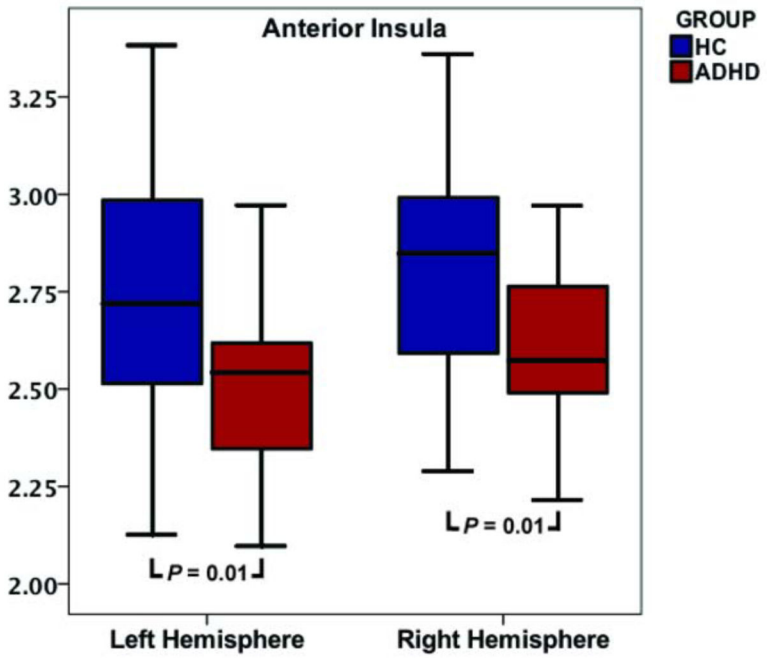

Figure 2.

Box plot of the Left and Right Adjusted Insula Volumes (mm^3) in ADHD and Healthy Controls

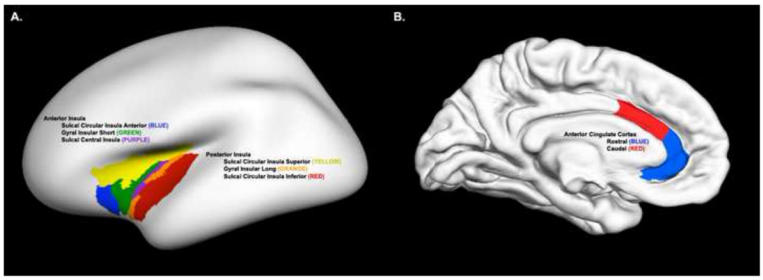

Figure 3.

Correlation of the Left Insula Adjusted Volume (mm^3) with the CBCL Rule-Breaking Behavior SubscaleT-scores

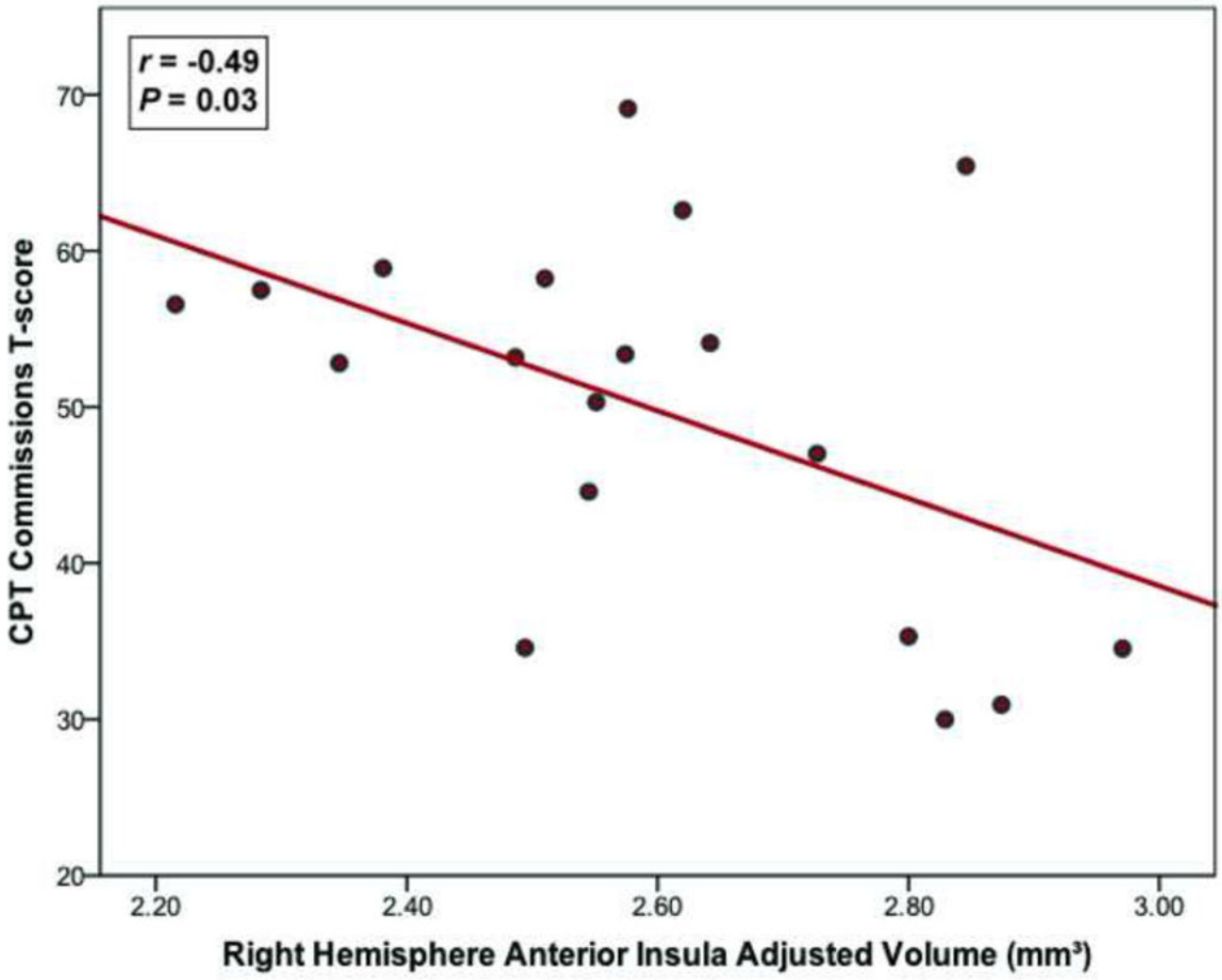

Figure 4.

Correlation of the Right Anterior Insula Adjusted Volume (mm^3) with the Continuous Performance Test Commissions T-scores

Table 1

Demographic and clinical characteristics of children and adolescents diagnosed with ADHD and healthy controls with between group significance

	ADHD (*n* = 19)	HC (*n* = 25)	*p*- value
Female (%)	9 (47.37)	13 (52.00)	ns
Caucasian	16 (84.21)	23 (92.00)	ns
ADHD combined type	12 (63.16)	-	-
ADHD inattentive type	7 (36.84)	-	-
Family history of ADHD	12 (63.16)	-	-
Current stimulant therapy	12 (63.16)	-	-
Duration of stimulant therapy (months)	35.26 ± 34.47	-	-
History of stimulant therapy	6 (31.58)	-	-
Current dose of stimulant (mg/kg)	0.76 ± 0.31	-	-

	Mean	SD	Mean	SD	*p*- value
Age	14.00	2.43	14.28	2.73	ns
GAF	67.53	9.76	91.36	3.87	< .001
WASI Full scale IQ	106.05	9.77	114.36	8.55	< .010
CPRS[1, 2] Oppositional subscale t-score	60.00	14.94	43.29	3.43	< .001
CPRS Cognitive problems subscale t-score	70.28	12.80	45.46	4.42	< .001
CPRS Hyperactivity subscale t-score	71.61	18.50	46.00	4.68	< .001
CPRS DSM-IV: inattentive subscale t-score	71.72	12.90	44.96	4.76	< .001
CPRS DSM-IV: hyperactive-impulsive subscale t-score	69.83	18.08	46.17	4.00	< .001
CPRS DSM-IV: total	74.22	14.83	45.04	3.63	< .001
CBCL[1] Attentional subscale t-score	68.05	9.18	50.79	1.22	< .001
CBCL Rule-breaking subscale t-score	61.42	8.56	52.08	3.88	< .001
CBCL Internal t-score	57.42	12.95	44.71	7.56	< .001
CBCL External t-score	60.53	11.12	42.17	6.54	< .001
CBCL Total t-score	62.42	9.36	41.50	7.81	< .001
CPT Omissions t-score	53.59	10.50	50.95	12.30	ns
CPT Commissions t-score	49.95	11.90	45.90	9.63	ns
CPT Hit rate t-score	56.27	13.16	54.18	10.94	ns

ADHD = Attention Deficit Hyperactivity Disorder; HC = Healthy Control; SD = Standard Deviation; GAF = Global Assessment of Functioning; WASI = Wechsler Abbreviated Scale of Intelligence; BIS = Barratt Impulsiveness Scale;

CPRS = Connors' Parent Rating Scale; CBCL = Child Behavior Checklist; CPT = Continuous Performance Test

[1] HC (n = 24);

[2] ADHD (n = 18)

Table 2

Between group differences in insular and ACC volumes (mm3) after adjusting for brain segmented volume.

Group Structure	ADHD (*n* =19)		HC (*n*=25)			
	Mean	**SD**	**MEAN**	**SD**	***Significance***	**Cohen's *d***
Left Hemisphere						
Total Anterior Insula	2.51	0.23	2.75	0.30	F(1,40)=8.09, *p*=0.01	0.90
Circular Anterior Insula Sulcus	0.73	0.12	0.86	0.11	F(1,42)=14.52, *p*<0.001	1.16
Insular Short Gyrus	1.64	0.18	1.67	0.23	ns	0.15
Central Insula Sulcus	0.14	0.05	0.22	0.11	F(1,42)=7.60, *p*=0.01	0.92
Total Posterior Insula	5.16	0.38	5.21	0.42	ns	0.13
Circular Superior Insula Sulcus	2.32	0.15	2.44	0.27	F(1,42)=3.15, *p*<0.08	.054
Insular Long Gyrus	0.70	0.16	0.64	0.15	ns	0.40
Circular Inferior Insula Sulcus	2.14	0.25	2.12	0.27	ns	0.08
Rostral ACC Gryus	1.86	0.36	2.01	0.38	ns	0.41
Caudal ACC Gryus	1.54	0.49	1.61	0.38	ns	0.17
Right Hemisphere						
Total Anterior Insula	2.59	0.21	2.84	0.30	F(1,40)=8.77, *p*=0.01	0.96
Circular Anterior Insula Sulcus	0.91	0.12	0.96	0.18	ns	0.33
Insular Short Gyrus	1.53	0.21	1.73	0.27	F(1,42)=7.22, *p*=0.01	0.83
Central Insula Sulcus	0.16	0.08	0.15	0.08	ns	0.13
Total Posterior Insula	4.28	0.25	4.23	0.40	ns	0.15
Circular Superior Insula Sulcus	1.81	0.18	1.84	0.25	ns	0.14
Insular Long Gyrus	0.82	0.14	0.72	0.15	F(1,42)=5.4, *p*=0.03	0.70
Circular Inferior Insula Sulcus	1.65	0.19	1.67	0.23	ns	0.10
Rostral ACC Gryus	1.52	0.22	1.44	0.30	ns	0.30
Caudal ACC Gryus	1.72	0.37	1.79	0.45	ns	0.17

SD=Standard Deviation; ACC=Anterior Cingulate Cortex