Reduced insular volume in attention deficit hyperactivity disorder

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**A B S T R A C T**

The aim of this study was to evaluate whether structural differences in the insula and anterior cingulate cortex (ACC), two critical areas of the “salience network,” co-exist in adolescents with attention deficit hyperactivity disorder (ADHD) compared with 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 3 T 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.

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 reported both in children and adults with ADHD (Makris et al., 2007; Narr et al., 2009; Seidman et al., 2011, 2006; Shaw et al., 2006). Task-based functional magnetic resonance imaging (fMRI) 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. It provides this information to other brain regions in order to guide appropriate behavioral responses to those 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 information 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 ACC has been proposed to play a critical role in switching between two 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.,
For instance, Hynd et al. (1993) 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. A subsequent study by Filipek et al. (1997) did not find differences in left or right total insular volumes when they compared 15 healthy control (HC) youths and 15 youths with ADHD.

More recently, advanced imaging techniques have found insular abnormalities in several neuropsychiatric illnesses. For example, in a voxel-based morphometry analysis, Sterzer et al. (2007) 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 neuromedical 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 dorsal ACC (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 et al. (2008), which compared 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.

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,” are 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 differed between adolescents with ADHD and HC compared to healthy controls (HC). The Child Behavior Checklist (CBCL) has been utilized frequently to assess internalizing 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 advertising. Study subjects were aged 10–18 years old, male or female, right-handed, of any race or ethnicity. Inclusion criteria for ADHD subjects included: major sensorimotor impairments (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 legal guardians (or legal guardian in the case of court-appointed guardians) provided written informed consent. A total of 22 youths with ADHD and 26 HC were recruited for this 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, 19 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 (GAF) was used to assess global functioning (American Psychiatric Association, 1994). All participants 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 (FSIQ).

2.2. Magnetic resonance imaging

Structural imaging was performed at the Utah Center for Advanced Imaging Research (UCAIR) using a 3 T Siemens Trio scanner. Structural acquisitions include a T1-weighted 3D MPRAGE grappa sequence acquired sagittally, with TE/TR = 1.8/2300 ms, 128 × 192 acquisition matrix, 256 × 256 matrix, 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 subject’s cortical thickness was estimated within the FreeSurfer image analysis environment (http://surfer.nmr.mgh.harvard.edu) (Dale et al., 1999; Fischl et al., 1999a, 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 mm × 1 mm × 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 representation of the gray–white matter 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. An individual subject’s cortical thickness was normalized to the spherical-space standard curvature template with a macaque deformable prior and the 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 et al. (2010) to produce gyral and sulcal cortical thickness and volumetric quality. Control quality was performed by a trained operator (JRB) throughout MR imaging processing within the FreeSurfer environment via manual visual inspection of each subject’s output to ensure proper Talairach registration, skull stripping, cortical surface reconstruction, and subcortical segmentation to ensure output integrity.

The Destrieux parcellation data included 2 gyrus and 4 sulcal output data for the insula and the frontal gyrus and sulcus. 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 these 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; Bourgon, 1999). Three regions were utilized to define the anterior insula and three regions were chosen to define the posterior insula as follows: the anterior insula included the insular part of the superior part of the insula and the sulcal part of the insula anterior (see Fig. 1). The posterior insula was defined as the sulcal part of the insula superior, the sulcal part of the insula inferior, and the gyrus insular. These insula subregions were obtained from the Destrieux 2005 atlas and include both gyrus and sulcal measurements. The central sulcus of the insula runs anterior-inferiorly from the superior segment of the circular segment of the insula and divides the insula into two parts: the short insular gyrus (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 three segments including the superior, anterior, and inferior. The anterior insula sulci limit the insula anteriorly from the orbital gyri and has been included in the anterior insula volume. The superior and inferior...
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