Psychiatry Research: Neuroimaging 204 (2012) 32–39

Contents lists available at SciVerse ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Reduced insular volume in attention deficit hyperactivity disorder

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ARTICLE INFO

Article history:
Received 19 December 2011
Received in revised form
20 July 2012
Accepted 21 September 2012

Keywords:
ADHD
Adolescents
Imaging
Cortical thickness
Insula

ABSTRACT

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.

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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 AIC 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.,

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0925-4927/$ - see front matter Published by Elsevier Ireland Ltd.
http://dx.doi.org/10.1016/j.pscychresns.2012.09.009

1993). 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 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 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. (2006), 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 externalizing symptoms in children with psychiatric illnesses (Achenbach and Rescorla, 2001). The Connors 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 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 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, 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, 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 (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/TI = 3.38 ms/2.0 s/1.1 s, 8° flip, 256×256 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 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, 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 $\times$ 1 mm $\times$ 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. An individual subject's cortical thickness was 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 et al. (2010) to produce gyral and sulcal cortical thickness and volumetric measures. 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 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; Duvernoy and Bourgouin, 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 short the central insula sulcus and the sulcal circular insula anterior (see Fig. 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 into 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 three 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