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Hemispheric brain asymmetry differences in youths with attention-deficit/hyperactivity disorder

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ABSTRACT

Introduction: Attention-deficit hyperactive disorder (ADHD) is the most common neurodevelopmental disorder in children. Diagnosis is currently based on behavioral criteria, but magnetic resonance imaging (MRI) of the brain is increasingly used in ADHD research. To date however, MRI studies have provided mixed results in ADHD patients, particularly with respect to the laterality of findings.
Methods: We studied 849 children and adolescents (ages 6–21 y.o.) diagnosed with ADHD ($n = 341$) and age-matched typically developing (TD) controls with structural brain MRI. We calculated volumetric measures from 34 cortical and 14 non-cortical brain regions per hemisphere, and detailed shape morphometry of subcortical nuclei. Diffusion tensor imaging (DTI) data were collected for a subset of 104 subjects; from these, we calculated mean diffusivity and fractional anisotropy of white matter tracts. Group comparisons were made for within-hemisphere (right/left) and between hemisphere asymmetry indices (AI) for each measure.
Results: DTI mean diffusivity AI group differences were significant in cingulum, inferior and superior longitudinal fasciculus, and cortico-spinal tracts ($p < 0.001$) with the effect of stimulant treatment tending to reduce these patterns of asymmetry differences. Gray matter volumes were more asymmetric in medication free ADHD individuals compared to TD in twelve cortical regions and two non-cortical volumes studied ($p < 0.05$). Morphometric analyses revealed that caudate, hippocampus, thalamus, and amygdala were more asymmetric ($p < 0.0001$) in ADHD individuals compared to TD, and that asymmetry differences were more significant than lateralized comparisons.
Conclusions: Brain asymmetry measures allow each individual to serve as their own control, diminishing variability between individuals and when pooling data across sites. Asymmetry group differences were more significant than lateralized comparisons between ADHD and TD subjects across morphometric, volumetric, and DTI comparisons.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is among the most common child-onset neurodevelopmental disorders worldwide, with an estimated childhood prevalence of ~5% (Swanson et al., 1998; Wolraich et al., 1996), and an economic burden estimated in the tens of billions of dollars per year (Pelham et al., 2007). Children with ADHD have problems with task prioritization (Qiu et al., 2011), and are more likely to have emotional problems including anxiety and depression. Adolescents with ADHD are at greater risk for automobile accidents, drug experimentation, and nicotine dependency (Schubiner, 2005).

Despite copious research, many aspects of the disease pathophysiology remain unknown. Furthermore, there is a large degree of behavioral heterogeneity within the diagnosis. Traditionally, the ADHD phenotype has been characterized along the domains of inattention, hyperactivity/impulsivity or a combination of both. In children,

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Table 1
Study Cohort Demographics.
Table 1. Summary of subject data for typically developing (TD), ADHD, and medication free ADHD participants by participating site. Medication free means no prior history of medication treatment for ADHD. Structural MRI data was included from the following sites: the Johns Hopkins Kennedy Krieger Institute (KKI), New York University (NYU), Oregon Health and Science University (OHSU), Peking University, and with diffusion tensor imaging (DTI) data from the University of California, Los Angeles (UCLA). Total indicated the total number of participants from that site. Female indicates the subset number, which were female. The medication free ADHD numbers reflect the subset of the total number of ADHD subjects that were medication naïve at the time of scanning. Handedness represents the percentage of subjects that were right handed. The subset number of ADHD subjects with comorbid oppositional defiant disorder (ODD) is also shown.

Diagnosis	Measure	Peking	KKI	NeuroImage	NYU	OHSU	Pittsburgh	WashU	UCLA
Typically developing									
	Total	116	61	23	99	42	89	61	17
	Female	45	27	12	52	24	43	28	11
	Age	11.7 ± 1.7	10.3 ± 1.3	17.3 ± 2.6	12.2 ± 3.1	8.9 ± 1.2	15.1 ± 2.9	11.5 ± 3.9	13.2 ± 2.0
	IQ	118.2 ± 13.3	111.5 ± 10.3	NR	110.4 ± 14.3	118.4 ± 12.6	109.8 ± 11.5	116.1 ± 14.1	110.4 ± 13.1
	Handedness	99.1	93.4	91.3	91.9	100.0	95.5	100.0	100.0
ADHD									
	Total	78	22	25	123	37	0	0	56
	Female	7	10	5	27	11	n/a	n/a	17
	Age	12.4 ± 2.0	10.2 ± 1.6	16.7 ± 2.9	11.1 ± 2.7	8.8 ± 1.0	n/a	n/a	12.6 ± 3.2
	IQ	105.4 ± 13.2	106.0 ± 15.2	NR	106.3 ± 14.3	108.5 ± 13.9	n/a	n/a	106.2 ± 13.1
	Handedness	97.4	90.1	96.0	97.6	100.0	n/a	n/a	NR
	ODD	25	6	NR	5	4	n/a	n/a	27
ADHD medication free									
	Total	52	16	NR	32	20	n/a	n/a	29
	Female	6	7	NR	10	5	n/a	n/a	8
	Age	12.7 ± 1.9	10.6 ± 1.6	NR	10.2 ± 2.3	8.8 ± 0.7	n/a	n/a	12.6 ± 3.8
	IQ	104.0 ± 12.4	107.9 ± 14.7	NR	106.9 ± 13.5	108.6 ± 13.8	n/a	n/a	106.1 ± 13.9
	Handedness	98.1	93.8	NR	96.6	100.0	n/a	n/a	NR
	ODD	14	4	NR	2	4	n/a	n/a	0

diagnosis typically is made by integrating clinical information derived from parents and teachers, and standardized ratings of ADHD presentations (McGough and McCracken, 2000). Diagnosis also hinges on the degree to which these persistent behavioral traits interfere with daily life in multiple settings including school, home, and/or work. A quantitative biomarker for the disease would be highly beneficial for diagnostic and therapeutic assessments.

Over the past decade, high-resolution magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) have been increasingly used to study anatomic differences in the ADHD brain. Nonetheless, imaging studies thus far have yielded varied results (Narr et al., 2009). For example, recent meta-analyses of structural differences report global gray matter reduction in basal ganglia regions including: caudate, putamen, and globus pallidus (Ellison-Wright et al., 2008) as well as right lentiform nucleus with mixed findings with respect to laterality (Nakao et al., 2011). A recent mega analysis found smaller volumes in accumbens, amygdala, caudate, hippocampus, putamen and intracranial volume without significant changes in pallidum (Hoogman et al., 2017). Similarly, both the laterality and significance of DTI results have varied across studies (for review, see van Ewijk et al., 2012). Interestingly, structural brain signatures of ADHD appear to resolve to some extent over the course of development (Larisch et al., 2006; Castellanos and Proal, 2009), and with stimulant treatment that enhances dopamine (DA) signaling (Shaw et al., 2009b).

Here, we hypothesized that patterns of hemispheric asymmetry differences would be observed across structural neuroimaging measures in the ADHD population. To investigate this, we studied a large cohort of ADHD youths and age-matched typically developing (TD) participants using MRI and DTI imaging techniques to assess both within hemisphere measures, and asymmetries in brain volume, morphology, and white matter microstructure.

2. Methods

2.1. Study population

We used two sources of data for this investigation. The first data set included the publicly shared ADHD200 database. These data were collected as part of the Functional Connectomes Project (FCP) and the International Neuroimaging Data sharing Initiative (INDI) (Biswal et al., 2010) as part of a push for accelerated sharing of data and analytic resources in the imaging community (Milham, 2012). We used structural MRI data collected at eight participating sites from 776 individuals (491 TD, 285 ADHD, ages 7–21 years old). The demographic data included: age, sex, full-scale IQ, and handedness, any secondary diagnosis and medication status. Adolescents in the ADHD group met criteria for ADHD on the DICA-IV and had a T-score of 65 or greater on the Conners' Parent Rating Scale (CPRS-R) long form (DSM IV inattentive), or M (DSM IV hyperactive/impulsive), or met criterion on the DuPaul ADHD Rating Scale IV (six out of nine measures marked 2, or 3 for inattentive or hyperactive/impulsivity).

The second source of data included structural MRI and DTI data collected at UCLA. A total of 104 subjects (age 6–18 y.o.) participated in this study, approved by the UCLA Institutional Review Board, (see (Lawrence et al., 2013) for further detail). All children were evaluated for ADHD and other psychiatric diagnoses based on an interview with the primary caretaker, using a semi-structured diagnostic interview, the Kiddie-Schedule for Affective Disorders and Schizophrenia–Present and Lifetime version (K-SADS-PL) and a direct interview with the child if 8 years of age or older. Parents completed the Behavior Rating Inventory of Executive Function (BRIEF), and parental ratings on the Swanson, Nolan, and Pelham, Version IV (SNAP-IV) Rating Scale were used to supplement the diagnostic interviews. A total of 56 participants met diagnostic criteria for ADHD. Controls across all data sources did not meet diagnostic criteria for ADHD or any other current psychiatric disorder.

2.2. Inclusion criteria

Psychostimulant medication can alter brain structure; therefore, subjects in the ADHD200 study whose medication history was unspecified were excluded from further analysis. Three of the sites in the ADHD200 cohort did not report medication status; therefore subjects who met diagnostic criteria for ADHD from these sites were excluded