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Integrated analysis of gray and white matter alterations in attention-deficit/hyperactivity disorder

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ABSTRACT

Background: Magnetic resonance imaging (MRI) is able to provide detailed insights into the structural organization of the brain, e.g., by means of mapping brain anatomy and white matter microstructure. Understanding interrelations between MRI modalities, rather than mapping modalities in isolation, will contribute to unraveling the complex neural mechanisms associated with neuropsychiatric disorders as deficits detected across modalities suggest common underlying mechanisms. Here, we conduct a multimodal analysis of structural MRI modalities in the context of attention-deficit/hyperactivity disorder (ADHD).
Methods: Gray matter volume, cortical thickness, surface areal expansion estimates, and white matter diffusion indices of 129 participants with ADHD and 204 participants without ADHD were entered into a linked independent component analysis. This data-driven analysis decomposes the data into multimodal independent components reflecting common inter-subject variation across imaging modalities.
Results: ADHD severity was related to two multimodal components. The first component revealed smaller prefrontal volumes in participants with more symptoms, co-occurring with abnormal white matter indices in prefrontal cortex. The second component demonstrated decreased orbitofrontal volume as well as abnormalities in insula, occipital, and somato-sensory areas in participants with more ADHD symptoms.
Conclusions: Our results replicate and extend previous unimodal structural MRI findings by demonstrating that prefrontal, parietal, and occipital areas, as well as fronto-striatal and fronto-limbic systems are implicated in ADHD. By including multiple modalities, sensitivity for between-participant effects is increased, as shared variance across modalities is modeled. The convergence of modality-specific findings in our results suggests that different aspects of brain structure share underlying pathophysiology and brings us closer to a biological characterization of ADHD.

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder that consistently has been related to abnormalities in brain structure. Magnetic resonance imaging (MRI) provides insights into brain morphology and white matter mesostructure by means of high-resolution anatomical imaging and diffusion-weighted imaging. To date, analyses have focused on each data modality separately, thus limiting conclusions to the modality analyzed. Recent

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advances in analytic techniques support integration of different data modalities, allowing for a simultaneous multimodal characterization of the biological markers associated with neuropsychiatric disorders (Groves et al., 2011).

Focusing on single data modalities, ADHD has been associated with decreased cortical thickness of regions implicated in attentional processing and cognitive control, including the frontal lobe and anterior cingulate cortex (ACC) (Castellanos et al., 2002; Narr et al., 2009). In addition, maturation of cortical thickness is delayed in ADHD compared to controls, with a maturational lag of up to five years in the prefrontal cortex (Shaw et al., 2007). Cortical surface area (relative amount of areal expansion or compression) exhibits a similar developmental delay (Shaw et al., 2012). Yet, although anomalies in prefrontal cortical thickness in ADHD are consistent, divergent findings outside the prefrontal cortex have been reported. These include thinner bilateral medial temporal cortices and increased cortical thickness in left superior parietal cortex (Narr et al., 2009).

Brain volumetric analyses have associated ADHD with a 3–5% smaller total brain and gray matter volume compared to controls (Castellanos et al., 2002; Greven et al., 2015). Further, voxel-based morphometry (VBM) analyses in ADHD support results of smaller prefrontal volumes, more specifically of ACC (Frodl & Skokauskas, 2012), and reveal smaller volumes across several specific brain regions, most consistently in basal ganglia, thalamus, cerebellum, and amygdala (Frodl & Skokauskas, 2012; Plessen et al., 2006; Mackie et al., 2007; Nakao et al., 2011).

Alterations in the brain's white matter have frequently been reported in ADHD. While diffusion indices describe different aspects of white matter microstructure (e.g., fractional anisotropy [FA]; mean diffusivity [MD]; tensor mode [MO]), studies concerning ADHD have mainly focused on FA. Yet, the reported findings have been heterogeneous and widespread throughout the brain, possibly because of region of interest approaches, variation in analysis techniques, and small sample sizes. A recent meta-analysis reported altered FA associated with ADHD in the tracts of the fronto-striatal-cerebellar circuit (van Ewijk et al., 2012).

The heterogeneity of imaging-based findings in ADHD, as described above, negatively impacts on our ability to interpret modality-specific results in the biological context of underlying pathophysiology. This is largely due to the isolated picture of brain abnormalities that is provided by unimodal univariate analyses. Recently developed analysis techniques allow integrative analyses across imaging modalities (Groves et al., 2011). Analyzing data in a multimodal way allows identification of co-occurring changes across brain measures, potentially reflecting shared pathophysiology and etiological processes. Importantly, this integrative approach does still allow for unimodal findings to be identified (Groves et al., 2012). Analyses integrating modalities add up to more than the sum of the modalities, as the integration of metrics increases sensitivity for between-participant effects by providing improved modeling of shared variance across modalities (Groves et al., 2012). While moving from uni- to multi-modal analysis permits the simultaneous characterization across different aspects of biological change measured by different MR modalities, the uni- to multi-variate change permits the simultaneous characterization across different brain areas, i.e., within distributed networks. Here, we conducted a multivariate multimodal analysis in a large and well-characterized ADHD sample through combining gray matter probability, cortical thickness, surface area volume estimates, and white matter diffusion indices.

2. Materials and methods

2.1. Sample

We included 333 participants from the NeuroIMAGE study (www.neuroimage.nl) (von Rhein et al., 2014), the Dutch follow-up of the International Multicenter ADHD Genetics (IMAGE) study (Muller et al., 2011a; Muller et al., 2011b). Participants with ADHD combined type and their siblings (regardless of ADHD diagnosis) were recruited from outpatient psychiatric or pediatric clinics. Control families were recruited from schools and did not meet criteria for ADHD, neither did their first-degree relatives. Further inclusion criteria in IMAGE were an IQ ≥ 70, European Caucasian descent, and no diagnosis of autism, epilepsy, general learning difficulties, brain disorders, or known genetic disorders (such as Fragile X or Down syndrome). Diagnostic, neurocognitive, MRI, and genetic data for NeuroIMAGE were collected at the VU University Amsterdam and Radboudumc Nijmegen. All participants and their parents (in case of participants below 18 years of age) gave informed consent and the study was approved by local ethical committees. For the current analyses we selected all participants that had both diffusion tensor imaging (DTI) and structural T1 scans of good quality as assessed by visual inspection ($n = 333$). Participants were divided into two groups based on the presence of an ADHD diagnosis (129 ADHD and 204 non-ADHD; Table 1). There were no differences between the participants included in the current analysis and the complete NeuroIMAGE sample on measures of ADHD severity, age, and gender ($p > 0.05$).

2.2. Diagnostics

To determine ADHD diagnoses, all participants were assessed using a combination of a semi-structured diagnostic interview and Conners' ADHD questionnaires. Participants were administered the ADHD section of the Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime Version (Kaufman et al., 1997), carried out by trained professionals. Both the parents and the child, if ≥12 years old, were interviewed separately and were initially only administered the ADHD screening interview. Participants with elevated scores on any of the screen items were administered the full ADHD section. Further each child was assessed with a teacher-rating (Conners' Teacher Rating Scale - Revised: Long version (CTRS-R:L); (Conners et al., 1998); applied for children <18 years) or a self-report (Conners' Adult ADHD Rating Scales - Self-Report:Long Version (CAARS-S:L); (Conners et al., 1999); applied for children ≥18 years). A diagnostic algorithm was applied to combine symptom counts on the K-SADS and CTRS-R:L (for participants <18 years) or CAARS-S:L (for participants ≥18), providing operational definitions of each of the 18 behavioral symptoms of ADHD defined by the DSM-IV (American Psychiatric Association, 2000). Symptoms of the CTRS-R:L or CAARS-S:L were only used in the algorithm if at least 2 symptoms were reported on this questionnaire. Participants with a combined symptom count of ≥6 symptoms of hyperactive/impulsive behaviour and/or inattentive behaviour were diagnosed with ADHD, provided they: a) met the DSM-IV criteria for pervasiveness and impact of the disorder (measures derived from the K-SADS), b) showed an age of onset before 7, derived from the K-SADS, and c) received a $T \geq 63$ on at least one of the DSM ADHD scales on either one of Conners' ADHD questionnaires. Criteria were slightly adapted for young adults (≥18 years), such that a combined symptom count of 5 symptoms was sufficient for a diagnosis (Kooij et al., 2005), also in accordance with the ADHD algorithm in DSM-5. Participants not meeting the criteria for an ADHD diagnosis were assigned to the non-ADHD group. For participants using stimulant medication, participants were asked to fill out the questionnaires keeping a period of time when they were off medication in mind. For the testing day, participants were asked to withhold the use of psychoactive medication for 48 h before visit.

Comorbidity with oppositional defiant disorder (ODD) and conduct disorder (CD) was assessed using the K-SADS. Initially only the screening interview was administered, thereafter participants with elevated scores on any of the screen items were also administered the full section.

2.3. MRI acquisition

MRI scans were acquired at two different locations (Donders Centre for Cognitive Neuroimaging in Nijmegen, The Netherlands and VU