Archival Report

Biological Psychiatry

Discrete Global but No Focal Gray Matter Volume Reductions in Unmedicated Adult Patients with Attention-Deficit/Hyperactivity Disorder

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ABSTRACT

BACKGROUND: Gray matter reduction mainly in the anterior cingulate cortex, the basal ganglia, and the cerebellum has been reported in attention-deficit/hyperactivity disorder (ADHD). Yet, respective data remain contradictory and inconclusive. To clarify if structural alteration in these brain areas can be verified in a large cohort of adult patients and if a history of stimulant medication has an effect on brain structure, magnetic resonance imaging was performed in the context of a clinical trial on the efficacy of group psychotherapy, clinical management, methylphenidate, and placebo (Comparison of Methylphenidate and Psychotherapy in Adult ADHD Study Trial).

METHODS: Between January 2007 and August 2010, 1480 patients from seven study centers across Germany, aged 18 to 58, were prescreened; 518 were assessed for eligibility; 433 were randomized; and 187 were eligible for neuroimaging. The control group included 121 healthy volunteers. Structural magnetic resonance imaging data sets were acquired. Following strict quality control, 131 patient and 95 control data sets could be analyzed. All patients were unmedicated for at least 6 months. The established method of voxel-based morphometry (VBM8 segmentation and diffeomorphic anatomical registration through exponentiated lie normalization) was used to assess global and regional brain volumes.

RESULTS: Patients displayed subtle global cerebral volume reductions. There was no evidence of regional gray matter volume abnormalities. The inattentive ADHD subtype was linked to smaller volumes in the left dorsolateral prefrontal cortex. A history of previous medication did not modulate brain volumes.

CONCLUSIONS: ADHD in adulthood is associated with global rather than regional volumetric abnormalities. Previous use of stimulant medication does not seem to modify subsequent brain volumes in a significant way.

Keywords: Adults, Attention-deficit/hyperactivity disorder, Brain imaging, Combined subtype, Inattentive subtype, Voxel-based morphometry

http://dx.doi.org/10.1016/j.biopsych.2015.05.012

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder (1) with an estimated prevalence in adulthood of 2.5% to 4.9% (2,3). DSM-IV distinguishes the predominantly inattentive ADHD (iADHD), the mainly hyperactive-impulsive ADHD, and the combined subtype ADHD (cADHD) (4), while the ICD-10 equivalent, hyperkinetic disorder (5), does not recognize these subtypes (1,6,7).

ADHD runs in families (8,9), but nongenetic acquired risk factors like lead exposure, preterm birth, antenatal and perinatal pregnancy complications, and antenatal exposure to alcohol or nicotine also contribute to the etiology (10,11). Dysexecutive symptoms like disinhibition, working memory deficits, problems in set shifting, deficient sustained attention, planning problems, and lack of effortful control belong to the core features of ADHD (12–16). They are neuroanatomically subserved by the so-called prefronto-striato-thalamo-frontal re-entry circuits (17,18). Abnormalities in these circuits have been reported in several brain imaging studies (19–22).

Previous Findings in structural imaging in adult ADHD

In Table 1, we summarize all published voxel-based morphometry (VBM) studies on adult ADHD, as well as respective available meta-analyses for children and adolescents. It shows that the pattern of findings is ambiguous. Nevertheless, it provides three important insights. First, the reported structural abnormalities are distributed over several distinct anatomical areas (Table 1). Second, none of these structural abnormalities are consistently altered across all studies (23,24; Table 1). Third, meta-analyses show that alterations in some core areas like the basal ganglia (in particular the caudate nucleus, the

ISSN: 0006-3223

Table 1. Summary of Findings of Previous Structural Imaging Studies on Adult ADHD and Findings in Meta-analyses on Childhood and Adolescence ADHD

Author	Year	Sample: *n* Patients/ *n* Control Subjects	Mean Age Patients/ Control Subjects	Male Ratio (%) Patients/ Control Subjects	Ratio of Treated Patients (%)	Global Findings	Regional Findings
Voxel-Based Morphometry Studies in Adult ADHD							
Almeida Montes *et al.* (25)	2010	20/20	28.95/27.57	50/50	0	Not reported	GM reduction in the right caudate
Depue *et al.* (41)	2010	31/21	20/19.3	61.1/48.9	77.4	No difference in global GM	Reduced GM volume in the right inferior frontal gyrus
Ahrendts *et al.* (40)	2011	31/31	31.2/31.5	65/65	0	Overall brain volume on average 1.1% smaller but not significant	Normal prefrontal, striatal, and parietal GM; GM reduction bilaterally in the visual cortex
Amico *et al.* (48)	2011	20/20	33.6/34.7	75/75	30	No difference in global GM and WM	GM reduction in the right and left anterior cingulate cortex
Almeida Montes *et al.* (52)	2011	10/10	27.9/26.5	0/0	0	Not reported	Reduced GM density in the right cerebellar hemisphere in combined subtype ADHD
Proal *et al.* (24)	2011	59/80	41.1/41.3	100/100	97	Mean cortical thickness significantly reduced	GM decreased in the right caudate, right thalamus, and bilateral cerebellar hemispheres
Seidman *et al.* (23)	2011	74/54	37.3/34.3	51/46	69 (lifetime) 28 (current)	Not reported	No significant differences following correction for multiple testing, left caudate GM reduction following region of interest based analysis
Makris *et al.* (28)	2013	24/24	36.8/36.8	62.5/62.5	0	Not reported	Volume decrease in cerebellum
Onnink *et al.* (26)	2014	119/107	36.3/36.9	38.66/42.1	76	No difference in global GM and WM	Reduced right caudate volume only for male subjects
Pironti *et al.* (53)	2014	20/20	32.2/32.6	75/65	80	No difference in global TBV and ICV	Decreased GM in right inferior-frontal gyrus; increased GM volume in the left middle occipital gyrus, right superior occipital gyrus, and left dorsal mid cingulate cortex; increase in white matter volume right inferior fronto-occipital fasciculus
Meta-Analyses in Adult ADHD							
Nakao *et al.* (adult subsample) (20)	2011	176/146	31.8/30.7	59/53	29	Significantly smaller global GM volumes; difference was more pronounced when adult study was excluded	No group difference
Frodl and Skokauskas (21)	2012	145/115	31.9/30.5	56.6/52.2	0–77.4	Not reported	Volume reduction in anterior cingulate cortex
Meta-Analyses in Childhood and Adolescence ADHD							
Valera *et al.* (42)	2007	565/583	11.0/11.3	81.2/81.3	Unclear	Abnormalities in TBV and right cerebral volume	Abnormalities in cerebellar regions, the splenium of the corpus callosum, and right caudate
Ellison-Wright *et al.* (27)	2008	114/143	Unclear	Unclear	Unclear	Not reported	GM reduction in the right putamen/globus pallidus
Frodl and Skokauskas (21)	2012	175/173	Unclear	Unclear	66–100	Not reported	Reduced right globus pallidus and putamen volume; decreased caudate volumes in manual tracing studies
Nakao *et al.* (20) (total mixed sample of childhood and adult ADHD)	2011	378/344	20.8/19.6	71/71	55	Global GM reduced	Volume reduction localized in the right lentiform nucleus extended to the caudate nucleus

ADHD, attention-deficit/hyperactivity disorder; GM, gray matter; ICV, intracranial volume; TBV, total brain volume; WM, white matter.