Grey matter abnormalities in adult attention deficit/hyperactivity disorder as measured with structural MRI

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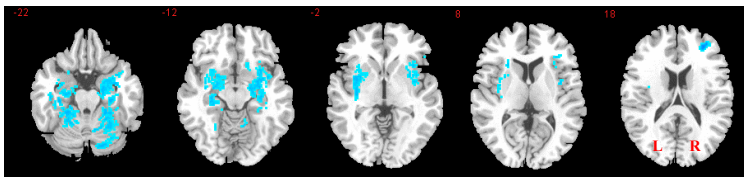
Introduction:

Attention deficit/hyperactivity disorder (ADHD) is the most prevalent psychiatric disorder in children and is characterized by inattention, impulsivity and/or hyperactivity. About 50 % of children diagnosed with this disorder continue to suffer symptoms at adulthood. An emerging neuroimaging literature has provided strong evidence for the involvement of key brain areas in the pathophysiology of this neurodevelopmental disorder [1]. However, the vast majority of magnetic resonance imaging (MRI) studies investigating structural brain abnormalities in ADHD were carried out in the pediatric population. To date, little is known about the persistence and stability of anatomical changes in ADHD across the lifespan. The aim of this study was to assess grey matter density in adult ADHD patients compared to healthy controls.

Methods:

16 adult patients diagnosed with ADHD with childhood onset and 17 healthy volunteers matched for age (30 ± 7 vs. 29 ± 6) and IQ (112 ± 9 vs. 116 ±4) were enrolled in the study. Patients were recruited from a psychiatric clinic specialized in adult ADHD and did not present any comorbid axis-I disorders. Half of the patients were ordinarily being treated with methylphenidate (n=7) or atomoxetine (n=1). Anatomic 3D T1 weighted images were obtained on a Siemens Trio 3T system (Siemens Medical Systems, Erlangen, Germany) with a gradient set capable of 45 mT/m and 200 T/m/s, and a 12-channel TIM head-coil. Images were acquired using a 3D magnetisation-prepared rapid gradient-echo (MPRAGE) pulse sequence (TR/TE/TI = 2300 ms/2.98 ms/900 ms, flip angle 9°, 1 average, 176 slices, 256 × 256 matrix size, 1×1×1 mm^3 voxel size). Volumes were spatially normalized and segmented into grey and white matter using the unified segmentation model of SPM5 [2]. In order to optimize this process [3] images were previously pre-processed using the following automated pipeline: 1.) skull-stripping was performed using the hybrid watershed algorithm or HWA [4] in FreeSurfer v.3.04, which integrates an atlas-based term constraining the shape of the brain; 2.) stripped volumes were then bias-corrected using the non-parametric non-uniform intensity normalization or N3 v.1.10 [5] with default arguments; 3.) a fine brain extraction that excludes venous sinuses and cerebro-spinal fluid (CSF) was performed using the brain extraction tool v.2.1 or BET2 [6] in FSL v.3.3 with fixed arguments: fractional intensity threshold, *f*, set to 0.4 and vertical gradient, *g*, set to 0. Non-parametric between-group analysis of grey and white matter segmented maps in standard space was undertaken using Cambridge Brain Analysis v2.3.0. Case-control differences in grey matter were estimated by fitting an analysis of covariance (ANCOVA) model at each intracerebral voxel in standard space. The null hypothesis of no differences in brain structure between the two groups was tested by applying a threshold of $\beta < 0.05$ to the resulting voxel statistic maps to generate clusters of spatially contiguous suprathreshold voxels. Cluster mass, i.e. the sum of suprathreshold voxel statistics in each 3-D cluster, was assessed by repeated random resampling of the data. The results of 10 permutations at each voxel were pooled over all intracerebral voxels, as described into detail elsewhere [7, 8]. This procedure generated a set of observed suprathreshold voxel clusters in three-dimensions the sum of suprathreshold voxel statistics it comprised. The mass of each cluster was tested against a null distribution of 3D cluster mass sampled by applying the same procedure to the β maps after permutation. For each between-group comparison, we used probability thresholds for cluster-level testing such that the average expected number of false positive tests was < 1. Clusters showing significant between-group differences were then described in terms of the Automated Anatomical Labeling (AAL) template image (reported where voxels/region > 20) [9]. Correlational analyses were undertaken between total cluster densities and disease severity in the adult ADHD patient group using Pearson's method. Total intracranial volumes (TIVs) were calculated following methods described elsewhere [10].

Results and Discussion:



CAMBA analysis identified six clusters in which grey matter differed between the groups. These withstood a stringent correction of <1 false positive clusters. Patients showed reduced grey matter density in distributed circuitries including the right inferior and middle frontal cortex, as well as bilateral putamen, hippocampus, amygdala and cerebellum (see Figure). A similar analysis with TIV as covariate yielded similar results.There was no significant difference groups in total intracranial volume (TIV) (mean ADHD 1.591+/-0.119, controls 1.513+/-0.151) (p>0.10). The here reported findings add to a growing body of evidence, mainly from the functional neuroimaging literature, implicating abnormalities in fronto-striatal and fronto-cerebellar circuitries in ADHD [11]. This network consists of parallel circuits that sub-serve motor, cognitive as well as emotional behaviors. The reduction in grey matter density found in the right inferior frontal gyrus may underlie the deficient inhibitory control characteristic of both children and adults with this disorder [12, 13]. Even though adults diagnosed with ADHD often exhibit difficulties in regulating their mood, anger and affect, circuits involving limbic structures have in contrast received relatively little attention in ADHD [14]. Here we provide, for the first time, compelling evidence of decreased grey matter density in bilateral hippocampus, amygdala and insula in adults suffering from ADHD, providing a neural basis for the mood dysregulation and irritability that is often observed in adults with ADHD.

References:

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