

Inter-subject comparison of fractional anisotropy in attention-deficit/hyperactivity disorder

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Introduction

Attention-deficit hyperactivity disorder (ADHD) is one of the most common neuropsychiatric disorders in children with a worldwide prevalence recently reported to be 5.29% [1]. Despite the pathophysiology of ADHD remaining unclear, structural imaging studies [2] have suggested significantly smaller volumes of ADHD subjects in dorsolateral prefrontal cortex, caudate, pallidum, corpus callosum, cerebellum, and total gray/white matter. In addition, the abnormality of white matter was further investigated by using diffusion tensor imaging either on a pre-selected region-of-interest manner [3] or an approach of whole-brain normalization [4, 5]. However, discrepancy was found in results of limited literature. The purpose of this study is to examine the fractional anisotropy (FA) of white matter in ADHD adolescents by the use of different algorithms of inter-subject comparison, which includes the well-known voxel-based morphometry (VBM) method [4] and tract-based spatial statistics (TBSS) [5].

Materials and Methods

The case group was recruited through the outpatient service of the Department of Psychiatry at our hospital while the control group was from the community. Subjects were diagnosed through a semi-structured clinical interview using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic Version, by a child psychiatrist (PY). In this study, the case group met DSM-IV diagnostic criteria for ADHD (inattentive, hyperactive/impulsive or combined subtype), while the control adolescents were ascertained to be free of any axis I diagnoses. Our subjects consisted of 26 male adolescents: 12 ADHD patients (average age of 14.8 years, range: 12.7-16.8 years) and 14 age-matching control subjects (average age of 15.7 years, range: 13.5-17.2 years). The documents of informed consents were signed by all subjects and their parents. This study was approved by both the Institutional Review Boards of our hospitals.

The experiments were conducted on a 1.5 Tesla scanner (Signa, GE Healthcare, Milwaukee, WI) with an 8-channel phased array head coil. Twice-refocused spin-echo diffusion sequence was performed with the following parameters: TR = 10 sec, TE = 93.4 msec, matrix size = 128×128, FOV 280 mm, NEX = 2, thickness = 4.4 mm, and 33 axial slices for whole-brain coverage. One $b=0$ image and 15-directional diffusion weighting images with a b value of 1000 sec/mm^2 were acquired. After eddy current correction using affine alignment, the diffusion tensor was estimated, following which the rotationally invariant FA was derived and taken as a marker of fiber tract integrity.

The inter-subject comparison throughout the whole brain was achieved independently by two algorithms, VBM and TBSS, as following. In our VBM-based normalization, individual $b=0$ volume was first non-linearly aligned to a pre-selected template which is the most representative one in the entire group, and all registered volumes were averaged to obtain a new template. For each subject, a non-linear transformation matrix was then determined according to this new template, and was applied on $b=0$ and diffusion weighted data as well, followed by estimation of FA values. In TBSS [6], individual FA maps were non-linearly aligned to the pre-selected FA template without spatial smoothing to generate the group mean FA map, which produced the white matter skeleton. Then FA values from normalized individual were projected to this standard skeleton using a local maximum approach. Notice that group analysis was restricted on the skeleton mask in TBSS when the two-sampled t-test was performed on the whole brain in VBM. A permutation-based method was adapted for multiple-comparison correction because the distribution of FA values on white matter is unknown. Significant difference was reported when $t > 3.5$ and the corrected- p value < 0.5 . An extra normalization to MNI152 template (size: $1 \times 1 \times 1 \text{ mm}^3$ voxel) was also implemented in both methods for convenient comparison.

Results

Significant decrease of FA was observed on white matter tracts widespread in a scattering pattern (Figure 1) by the use of both methods (VBM and TBSS) in patients compared to control group. Since significant test was carried out only on the white matter skeleton in TBSS instead of the whole brain region in VBM, minimal cluster sizes were set unequally to be 200 and 50 voxels for VBM and TBSS respectively to avoid false positive results. Figure 1 shows several regions where VBM and TBSS results find agreement (marked in yellow), including middle cerebellar peduncle (a), left inferior longitudinal fasciculus (b), superior longitudinal fasciculus (c), superior region of corona radiata (d), internal capsule (e), external capsule (f), optic radiation (g), and corpus callosum splenium (h). In addition, no region indicating larger FA in ADHD group was observed in our case (not shown), whether VBM or TBSS was used for normalization, which also agrees with the finding in [3, 4] but conflicts with [5].

Discussions

In contrast to VBM aiming for whole-brain comparison, group analysis via TBSS is performed on the local FA data projected to the white matter skeleton. Interpretation of TBSS findings therefore demands caution particularly when specifying the areas that might be related to ADHD pathophysiology. Regions showing decreased FA depicted consistently by both algorithms suggest validity, whereas increased FA in ADHD [5] seems to be absent. In general, VBM seems to identify wider distribution of FA difference than TBSS, although the limited amount of data included in this current study precludes us from drawing any conclusions at this time. Whether the discrepancies are physiological or technical in origin awaits further investigations.

References: 1. Polanczyk G et al., *Am J Psychiatry*. 2007;164(6):942-8. 2. Seidman LJ et al., *Biol Psychiatry*. 2005;57(11):1263-72. 3. Makris N et al., *Cereb Cortex*. 2008;18(5):1210-20. 4. Ashtari M et al., *Biol Psychiatry*. 2005; 57(5):448-55. 5. Silk TJ et al., *Hum Brain Mapp*. 2009;30(9):2757-65. 6. Smith SM et al., *Neuroimage*. 2006;31(4):1487-505.

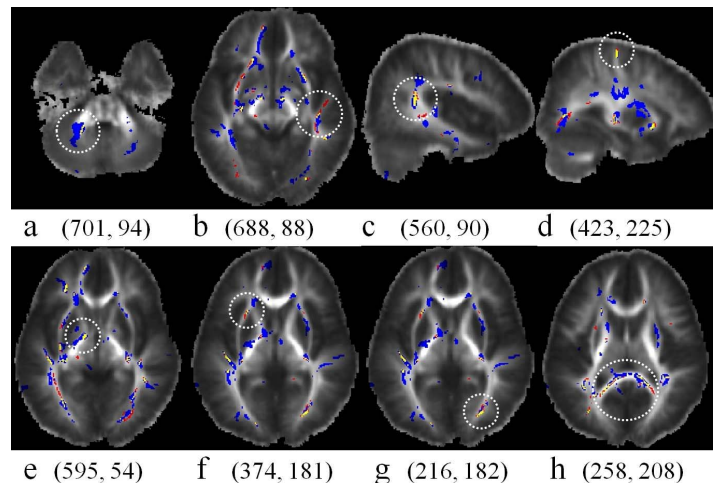


Fig.1 Significant difference in FA values (ADHD < control) detected by VBM only (blue), and by TBSS only (red), and by both methods (yellow) of inter-subject comparison was displayed on the mean FA in gray scale. Eight slices were selected to show scattering regions of significantly decreased FA mostly distributed on white matter tracts, which include middle cerebellar peduncle (a), left inferior longitudinal fasciculus (b), superior longitudinal fasciculus (c), superior region of corona radiata (d), internal capsule (e), external capsule (f), optic radiation (g), and splenium of corpus callosum (h). White dash circle are used to highlight the tract of interest. Next to each figure label is the cluster size detected using VBM and TBSS methods respectively.