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Diffusion imaging studies of Huntington's disease: A meta-analysis

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ABSTRACT

Background: Diffusion tensor imaging (DTI) could detect abnormal brain microstructural alterations. DTI studies of Huntington's Disease(HD) have yielded inconsistent results.
Objective: To integrate the existing DTI studies of HD and explore the validity of DTI to detect microstructural damages in HD brain via meta-analysis.
Methods: Systematic and comprehensive searches of the databases were performed for DTI studies of HD. The data from the studies that met our inclusion criteria were extracted and analyzed using the CMA2 software. Random effect models were utilized to minimize the potential between-study heterogeneity. One-way sensitivity analysis was conducted to test the robustness of the results.
Results: The meta-analysis included 140 pre-symptomatic HD (PreHD), 235 symptomatic HD (SymHD) patients and 302 controls, revealing significantly increased fractional anisotropy (FA) in the caudate, putamen, and globus pallidus, while decreased FA in the corpus callosum of both PreHD and SymHD patients compared with controls. In addition, significantly increased mean diffusivity (MD) was identified in the putamen and thalamus of both PreHD and SymHD patients, and in the caudate of SymHD patients, while no significant difference in MD in the caudate of PreHD patients. In the corpus callosum, there was a significant increase of radial diffusivity and axial diffusivity in SymHD patients compared with controls. Meta-regression showed gender-based difference in MD values of the caudate.
Conclusions: Our meta-analysis provides further evidence that DTI detects microstructural damage of both white matter and gray matter even in PreHD gene carriers. MD is less sensitive than FA in detecting structural changes in PreHD.

1. Introduction

Huntington's Disease (HD) is an autosomal dominant hereditary neurologic disease, caused by the abnormal expansion of CAG repeats in the *IT15* gene on chromosome 4 [1]. A number of expanded CAG repeats more than 36 can lead to neuronal death and brain atrophy, especially in the striatum [2]. The major clinical presentations of HD include motor dysfunction, cognitive impairment and psychiatric disorder [3].

The main pathology of HD is loss of medium spiny neurons, which are projection neurons, in the striatum. Loss of these projection neurons might cause white matter abnormality or microstructural alterations in the striatum. DWI or DTI could describe microstructural changes, which might precede macrostructural changes such as brain volume atrophy measured by voxel-based morphometry. Even though other imaging techniques are available, they have some limitations. For instance, functional MRI is dependent on the blood oxygenation level, which could only detect brain activity alterations instead of anatomical structural abnormality. PET studies were limited due to safety concerns about radiation exposure. DTI studies on HD have demonstrated that cognitive and psychiatric symptoms of HD patients are associated with disrupted structural striatal connections such as cortio-striatal circuits [4,5]. Through measuring diffusion parameters including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD), DTI could quantify the orientation and integrity of white matter (WM) tracts as well as offering insights into the microstructure of gray matter (GM) [6]. It is generally accepted that FA represents fiber coherence or directionality of the microstructure. FA is considered to be decreased with loss of tissue organization or cellular integrity, with a value of “0”

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suggesting equal diffusion in all directions whereas "1" suggesting unidirectional linear diffusion. MD estimates the average of the three principal directional diffusivities, with high MD value indicating unrestricted diffusion and low MD value indicating restricted diffusion [7]. RD and AD measure the rate of diffusion perpendicular and parallel to the main direction of diffusion, respectively. Increases in RD reflect the demyelination of WM tracts, while increases in AD represent axonal degeneration and loss [8].

In the field of DTI studies of HD, the caudate, putamen, globus pallidus (GP) and corpus callosum (CC) have been repeatedly investigated. However, they yielded inconsistent results possibly due to small sample size of each study. For instance, some studies reported increased FA in both caudate and putamen [9,10], while other studies reported significant FA changes only in the putamen, not in the caudate [11,12]. One study reported no significant difference in FA in the GP [13], while another reported significantly increased FA in the GP in HD [14]. Increased FA indicates increased integrity of the tissue. The mechanism underlying this remains unknown. A study on attention-deficit hyperactivity disorder reported increased FA in the striatum as well and implicated that it might be caused by anomalous WM development [15]. Currently, there are several interpretations of increased FA in the striatum in HD. One of them suggested that it correlated with preferential loss of the striatal connections, transforming the striatum into a more organized structure, as supported by Douaud et al. [9]. Another one suggested that it could result from pathologic processes that modify tissue integrity, such as neuronal remodeling and loss, secondary astrocytosis, or changes in cell permeability [11]. And a recent study implied that the increased FA observed in the GP of HD was likely due to an increased amount of metalloprotein-bound iron [13].

To figure out whether there are microstructural alterations measured by DTI parameters in HD brain, especially in the striatum, and to find out the most suitable parameter to detect the alterations, we carried out a systematic review of the literature of DTI studies on HD patients and conducted a meta-analysis using a similar processing method utilized by a published study on mild traumatic brain injury [16].

2. Methods

2.1. Literature search strategy

Systematic and comprehensive searches of the PubMed, Web of Science, Cochrane Library, and EMBASE databases were performed for DTI studies published between January 1946 and April 2016 that examined FA or MD of HD patients compared with HCs. The search keywords were ("Huntington's disease" OR "Huntington disease") AND ("white matter architecture" OR "microstructure" OR "diffusion tensor" OR "DTI" OR "tract-based spatial statistics" OR "TBSS"). The reference lists of the identified articles and review articles were also manually reviewed to search additional papers.

2.2. Selection criteria for the database

The articles that met the following inclusion criteria were adopted: (1) published in a peer-reviewed English language journal; (2) included genetically confirmed pre-symptomatic or symptomatic HD patients; (3) compared HD with HCs. Studies that are case reports or reviews were excluded.

2.3. Whole brain voxel-based analysis and region of interest analysis

Generally, there are two different approaches studying DTI parameters from DTI data. The first approach is called voxel-wise whole brain analysis (WBA), including voxel-based analysis (VBA) and tract-based spatial statistics (TBSS), which only provide the coordinates of the brain areas that show significantly difference in FA in patients compared to HCs. The other one is region of interest (ROI) analysis, including that used tractography for the definition of ROI [17]. This approach preselects brain structures to be studied based on a prior theory and reports values of the selected ROIs.

Our systematic search yielded seven studies using TBSS approach and four studies using VBA approach. Two of the seven TBSS studies are longitudinal, and four of them did not report coordinates. We emailed the authors, but they were not able offer the information. The four VBA studies used completely different thresholds, which is not suitable to conduct a meta-analysis. Thus, we will only conduct a meta-analysis of the ROI studies in the current work.

2.4. Selection of studies for meta-analysis

To select ROI studies from all the yielded articles, the following criteria was imposed for inclusion into the meta-analysis: (1) studies that adopted tractography or ROI methods; (2) studies provided sufficient data to allow for effect-size calculations; (3) studies that had recruited more than 9 pre-symptomatic (PreHD) or symptomatic HD (SymHD) patients for each group. We excluded papers that (1) included HD patients with other neurological disorders besides HD, (2) whose data were entered twice from a study population that had been analyzed in more than one publication. Brain regions were included if there were two or more studies reporting more than two datasets with sufficient data in total. If studies did not report sufficient data, we emailed the corresponding author to obtain further information. In cases where the author did not respond, we excluded the study from our analysis.

2.5. Data extraction

Two authors independently searched the literature, examined the retrieved articles, and extracted and cross- checked data. Cohen's d was calculated as the standardized mean difference (SMD) to define the effect size statistic. It is calculated as the difference between the mean of the experiment group and that of the comparison group divided by the pooled standard deviation. In our study, the mean values of DTI measures in the patient group were subtracted from that of the HC group in each selected brain area, and divided by the pooled standard deviation of both groups.

2.6. Statistical analysis

All the statistic analyses were carried out using the Comprehensive Meta-Analysis version2 software (2006, Biostat, Inc., Englewood, New Jersey, USA). A single SMD was computed from each comparison. In studies that separated multiple sub-regions from a single structure, for example, the caudate is segmented into head and body, or that reported DTI measures in the left and right hemispheres separately, the weighted average effect size was calculated and integrated in the analysis. In studies that reported two patient groups (PreHD and SymHD group), the weighted average effect size was also calculated and defined as the mean effect size of an additional combined HD group.

Random effect models were utilized for all the meta-analyses to minimize the potential between-study heterogeneity resulted from

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