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Voxel-based morphometry (VBM) studies in schizophrenia—can white matter changes be reliably detected with VBM?

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ABSTRACT

Voxel-based morphometry (VBM) is a hypothesis-free, whole-brain, voxel-by-voxel analytic method that attempts to compare imaging data between populations. Schizophrenia studies have utilized this method to localize differences in diffusion tensor imaging (DTI) derived fractional anisotropy (FA), a measure of white matter integrity, between patients and healthy controls. The number of publications has grown, although it is unclear how reliable and reproducible this method is, given the subtle white matter abnormalities expected in schizophrenia. Here we analyze and combine results from 23 studies published to date that use VBM to study schizophrenia in order to evaluate the reproducibility of this method in DTI analysis. Coordinates of each region reported in DTI VBM studies published thus far in schizophrenia were plotted onto a Montreal Neurological Institute atlas, and their anatomical locations were recorded. Results indicated that the reductions of FA in patients with schizophrenia were scattered across the brain. Moreover, even the most consistently reported regions were reported independently in less than 35% of the articles studied. Other instances of reduced FA were replicated at an even lower rate. Our findings demonstrate striking inconsistency, with none of the regions reported in much more than a third of the published articles. This poor replication rate suggests that the application of VBM to DTI data may not be the optimal way for finding the subtle microstructural abnormalities suggested in schizophrenia.

1. Introduction

Schizophrenia is a disease characterized, in part, by abnormalities in white matter that affect brain connectivity (Davis et al., 2003). It is not clear, however, whether these abnormalities affect the entire white matter equally, or if they are localized and limited to specific structures or connections. Both of these hypotheses have been suggested, and are frequently tested using a wide variety of in vitro and in vivo methods. Among those methods is diffusion tensor imaging (DTI), the first and so far the most powerful in vivo method that can be used to quantify the integrity of white matter (by means of the properties of water diffusion in human brain tissue) (Basser et al., 1994). DTI measures the diffusion of water molecules throughout the brain, including water in the cerebrospinal, intracellular, and extracellular fluids. Since ventricular spaces, gray matter, and white matter each have different structural properties, water diffusion in each respective region is likewise unique.

One measure that is of particular interest in DTI studies is fractional anisotropy (FA). FA is a measure of directional preference in water diffusion (Basser, 1995). As the axon bundles and myelin sheaths in the major fiber bundles of the brain cause water to preferentially diffuse parallel with the direction of the fiber bundle, FA can be interpreted as a measure of the integrity of the white matter in the area being investigated. Many different post-processing methods have been utilized to look at changes in FA in schizophrenic patients, with hopes of linking white matter abnormalities to the clinical symptoms seen in this devastating disease.

Post-processing and analytic techniques used for DTI data usually employ one of two approaches. The first approach is hypothesis-driven, where investigators focus on one or a few specific regions of the brain, defined by either manually placed regions of interest (ROIs), or extracted through a more automated means such as fiber tractography. The second approach is hypothesis-free and involves searching the entire brain in order to find regions (voxels) that differ between groups.

Articles taking the first approach have reported both global (or widespread) (e.g. Lim et al., 1999; Minami et al., 2003; Kumra et al., 2004; Mitelman et al., 2006) as well as local FA differences. The latter were reported to be limited to frontal connection abnormalities (Kitamura et al., 2005), interhemispheric connection abnormalities, such as the splenium of the corpus callosum (Foong et al., 2000), and fronto-temporal connection abnormalities, such as the cingulum bundle (Kubicki et al., 2003; Sun et al., 2003), uncinate fasciculus (Kubicki et al., 2002; Price et al., 2008), inferior occipito-frontal

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fasciculus (Rosenberger et al., 2008), superior longitudinal fasciculus (Jones et al., 2006), inferior longitudinal fasciculus (Ashtari et al., 2007), fornix (Zhou et al., 2008, Fitzsimmons et al., 2009), and anterior limb of the internal capsule (Buchsbaum et al., 2006; Oh et al., 2009).

Although the ROI and tractography approaches have produced significant results in terms of group differences, these results lack consistency and reproducibility. As already suggested in many previous reviews (i.e. Kubicki et al., 2007; Van Hecke et al., 2009), these inconsistencies possibly originate from a lack of methodological standards for data acquisition, post-processing, and analysis.

As opposed to hypothesis-based DTI analysis, voxel-based morphometry (VBM) is hypothesis-free and allows for an easy, highly automated, and relatively fast analysis of entire populations of subjects. For these reasons it is currently the most popular post-processing method used to compare DTI data across subjects. In this method, all subject scans are co-registered to a common atlas space. Then, images of patients are compared to images of controls voxel by voxel, and regions with statistically significant differences are reported. A number of DTI studies in schizophrenia have utilized VBM to look at differences in FA between patients and normal controls (see Table 1). Using this method, FA differences can be measured over the entire brain at once and, using a statistical threshold, differences in white matter integrity can be reported.

Despite the advantages of using VBM to look at DTI data, it is unclear how reproducible this method is since, until recently, there had been no systematic analysis of VBM studies in schizophrenia. Ellison-Wright and Bullmore (2009) recently published a meta-analysis of 15 different studies published to date, reporting FA reductions in the left frontal deep white matter and the left temporal deep white matter. For reasons presented below, we chose to use a different method of comparison between DTI VBM publications.

DTI VBM studies, unlike structural VBM studies, do not necessarily feature similar scanning and processing methods. More specifically, a variety of different scan parameters are used, as well as a variety of magnet strengths, image resolutions, numbers of diffusion directions, numbers of repetitions, ways of tensor estimation, and even slight differences in analytic parameters, all of which make it impossible to account for in a statistical meta-analysis comparison, such as the one by Ellison-Wright et al. previously mentioned. For these reasons, we sought to gain a clearer picture of the white matter abnormalities observed in schizophrenia as well as the reproducibility of DTI VBM studies by plotting the coordinates from 23 different articles, each utilizing the VBM analytic technique applied to schizophrenic populations, onto a single atlas and analyzing the distribution of observed abnormalities.

Table 1
Twenty-three DTI VBM studies in schizophrenia used in the analysis.

Author (date)	No. of patients/ controls	No. of coordinates	Atlas
Chronic schizophrenia studies			
Agartz et al. (2001)	15/15	2	Talairach
Ardekani et al. (2003)	14/14	13	Talairach
Buchsbaum et al. (1998)	5/6	3	Talairach
Burns et al. (2003)	30/30	3	Talairach
Hao et al. (2009)	34/66	3	MNI
Hubl et al. (2004)	26/13	17	Talairach
Kubicki et al. (2005)	21/26	10	Talairach
Mori et al. (2007)	42/42	10	MNI
Rametti et al. (2009)	25/24	1	MNI
Schlosser et al. (2007)	18/18	3	MNI
Seok et al. (2007)	30/22	6	Talairach
Shergill et al. (2007)	33/40	3	Talairach
Skelly et al. (2008)	25/25	7	Talairach
First-episode/early-onset schizophrenia studies			
Ashtari et al. (2007)	23/21	2	Talairach
Cheung et al. (2008)	25/26	7	Talairach
Hao et al. (2006)	21/21	17	MNI
Kumra et al. (2005)	26/34	1	Talairach
Kyriakopoulos et al. (2008)	19/20	3	MNI
Perez-Iglesias et al. (2010a)	62/54	4	Talairach
Perez-Iglesias et al. (2010b)	49/41	4	Talairach
Szeszko et al. (2005)	10/13	3	Talairach
Szeszko et al. (2008)	33/30	4	Talairach
White et al. (2007)	15/15	1	Talairach

2. Methods

We used the Medline and Ovid engines, searching for articles using "DTI" or "diffusion," "whole brain" or "voxel based" or "VBM," and "schizophrenia" as keywords. From among the results of these searches, we chose articles that used SPM for registration and reported reduced FA in schizophrenic patients compared to normal controls. Our review covers 23 articles (13 chronic; 10 first-episode/early-onset), all of which meet these criteria, published between February of 1998 and April of 2010.

For most articles, statistically significant coordinates representing reduced FA were extracted from tables or from the text. For articles with no points listed, coordinates were approximated by comparing the images in the articles showing highlighted regions of statistically significant FA reduction to the Talairach atlas using the Talairach Applet (www.talairach.org) and Sleuth v.1.1 (www.brainmap.org). Coordinates for all articles were initially extracted in their reported atlas space (or Talairach space if no points were listed), but were ultimately converted to Montreal Neurological Institute (MNI) atlas space. For this reason, as well as for reasons of consistency, only studies that used SPM for registration were selected and plotted. This led to the exclusion of articles from our original search query that used a newer voxel-based approach, introduced by Smith et al. (2006), tract-based spatial statistics (TBSS). Talairach coordinates were converted to MNI space using an affine transformation. Using 3D Slicer (www.slicer.org), we plotted the coordinates from the articles onto a single MNI atlas.

Cubes representing each coordinate were generated and labeled depending on whether the study was conducted with chronic or early-onset/first-episode patients. We chose to make each cube model $3 \times 3 \times 3$ voxels in size for the following reasons: 1) MNI atlas voxels are 1 mm^3, whereas most DTI data are about 2 mm × 2 mm × 2 mm at best. 2) Smoothing increases the size of clusters. 3) Actual cluster sizes were not reported in many of the articles. Finally, in order to quantify the percentage of studies reporting each white matter area, we used the MNI space white matter atlas (Laboratory of Neuro Imaging, 2008) to count the number of coordinates (models) that overlapped with each of the white matter structures (tracts).

3. Results

The coordinates representing reduced FA in patients with schizophrenia were scattered across the brain (Fig. 1). The genu of the corpus callosum, the splenium of the corpus callosum, the right anterior corona radiata, and the posterior thalamic radiation bilaterally (including the optic radiation) were the most consistently reported regions; however, each was reported in only six (26.09%; genu of the corpus callosum and left posterior thalamic radiation), seven (30.43%; right anterior corona radiata and right posterior thalamic radiation), or eight (34.78%; splenium of the corpus callosum) of the 23 articles reviewed. Other instances of reduced FA were replicated at an even lower rate.

When the results were grouped by time since diagnosis, results improved only marginally. One region was reported in five (38.46%) of the 13 chronic schizophrenia studies: the left posterior thalamic radiation (including the optic radiation). Likewise, first-episode and early-onset patient studies reported two regions in four of the 10 studies: the splenium of the corpus callosum and the right anterior corona radiata. In addition, 16 of the 23 articles (10 chronic; six early-