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White matter 'potholes' in early-onset schizophrenia: A new approach to evaluate white matter microstructure using diffusion tensor imaging

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ABSTRACT

There is considerable evidence implicating white matter abnormalities in the pathophysiology of schizophrenia. Many of the recent studies examining white matter have utilized diffusion tensor imaging (DTI) using either region of interest (ROI) or voxel-based approaches. Both voxel-based and ROI approaches are based on the assumption that the abnormalities in white matter overlap spatially. However, this is an assumption that has not been tested, and it is possible that aberrations in white matter occur in non-overlapping regions. In order to test for the presence of non-overlapping regions of aberrant white matter, we developed a novel image processing technique that evaluates for white matter 'potholes,' referring to within-subject clusters of white matter voxels that show a significant reduction in fractional anisotropy. We applied this algorithm to a group of children and adolescents with schizophrenia compared to controls and found an increased number of 'potholes' in the patient group. These results suggest that voxel-based and ROI approaches may be missing some white matter differences that do not overlap spatially. This algorithm may be also be well suited to detect white matter abnormalities in disorders such as substance abuse, head trauma, or specific neurological conditions affecting white matter.

1. Introduction

White matter (WM) tracts within the brain consist of myelinated neuronal fibers that serve as 'superhighways' for the rapid transfer of information between brain regions. Medical disorders that disrupt these pathways, such as multiple sclerosis or amyotrophic lateral sclerosis, can profoundly affect various aspects of cognitive and motor function (Gilmore et al., 2009). Schizophrenia is a severe mental illness that involves a constellation of clinical symptoms and global cognitive deficits. While the etiology of schizophrenia is yet unknown, one current hypothesis is a disruption in brain connectivity (Friston and Frith, 1995). Thus, cerebral WM has become a source of considerable investigation in schizophrenia, with recent evidence supporting WM abnormalities based on postmortem samples (Davis et al., 2003; Heckers et al., 1991; Karoutzou et al., 2008; Uranova et al., 2007), genetic analyses (Hakak et al., 2001), and diffusion tensor imaging (DTI) (Kanaan et al., 2005; Kubicki et al., 2007; Kyriakopoulos et al., 2008; White et al., 2008).

There are now close to 60 studies that have utilized DTI to assess WM microstructure in schizophrenia (White et al., 2008). What is most striking about the combined findings of these studies is the considerable heterogeneity in the locations of the WM differences between patients and controls (Kanaan et al., 2005; Kubicki et al., 2007; White et al., 2008). While there does appear to be an over-representation of abnormalities in the corpus callosum, cingulate bundle, and frontal WM, nearly every WM structure has been implicated. Since the majority of DTI studies utilize voxel-based techniques to evaluate regional WM differences, typically only positive findings are reported. However, the whole brain testing inherent in voxel-based approaches is also associated with wide-spread areas that do not demonstrate significant patient/control differences. These negative results complicate the interpretation of DTI findings in patients with schizophrenia.

While a few early studies have reported a diffuse pattern of WM abnormalities in patients with schizophrenia (Agartz et al., 2001; Flynn et al., 2003), most DTI studies tend to have focal abnormalities (White et al., 2008). Perhaps one explanation for the variability in the existing studies involves the methodologies applied to determine the underlying deficits. The current methodologies applied to DTI studies involve either region of interest (ROI) or voxel-based techniques. Both ROI and voxel-based approaches make an assumption that WM abnormalities are spatially localized to specific regions in patients. For

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example, for ROI or voxel-based approaches to detect an abnormality of the cingulate bundle, the WM deficit would need to be spatially localized to the same region of the cingulate bundle in most of the patients. However, a deficit could occur at different locations along the cingulate tract and have a similar contribution to the clinical deficit. While spatial smoothing can be applied to account for this variability (Jones et al., 2005), it is limited to regions that are proximally located (White et al., 2001). There have been recent studies using tractography approaches that support this weakness of ROI approaches (Kanaan et al., 2006).

It is possible that disruptions in WM integrity may occur at different 'points of weakness' in different individuals. Disorders such as tuberous sclerosis (Inoue et al., 1988; Makki et al., 2007) and multiple sclerosis (Gilmore et al., 2009) may have heterogeneity in affected WM pathways, and there may be similar heterogeneous patterns in the location of WM abnormalities in schizophrenia. While primary WM disorders may not be directly compared to schizophrenia, we only note the assumption of spatially overlapping regions has not been confirmed. In fact, the heterogeneity of the results in the current studies may be a result of the analytic strategies and voxel-based or ROI approaches, which are powerful for evaluating gray matter differences, but may not be as well suited to identify specific WM abnormalities.

The goal of this study was to evaluate a novel approach to examine WM abnormalities that does not require spatially overlapping deficits. Much in the way that we would not expect potholes to overlap when highways were placed one on top of another, we developed an algorithm to detect WM 'potholes.' A 'pothole' is a region of WM where a cluster of voxels falls significantly below its voxel-based mean. This algorithm was applied to a dataset of individuals with early onset schizophrenia (EOS), defined as those who develop the illness during childhood or adolescence. EOS has been shown to be on a continuum with the adult form of the illness (Rapoport et al., 1999; Rapoport and Inoff-Germain, 2000), although those with EOS tend to have greater genetic loading (Asarnow et al., 2001) and more pronounced negative symptoms (Frazier et al., 2007; Rabe-Jablonska and Gmitrowticz, 2000) than those with adult-onset schizophrenia.

2. Methods

2.1. Subjects

The participants included 29 patients (18 males and 11 females) with a diagnosis of schizophrenia ($n=22$), schizoaffective disorder ($n=4$), or schizophreniform disorder ($n=3$). The control group

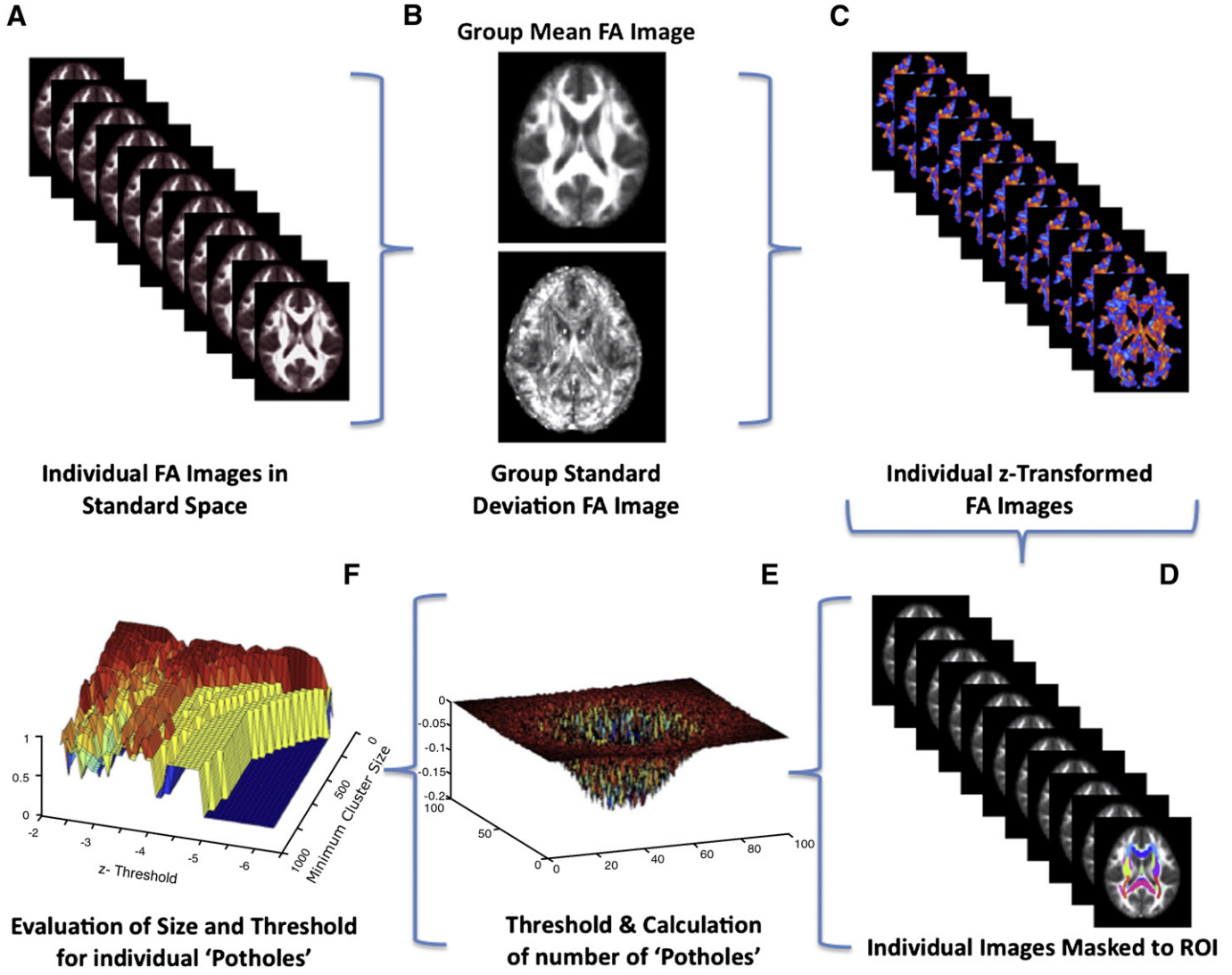

Fig. 1. Processing steps to determine white matter potholes. (A) FA maps of all subjects registered to MNI space using tract-based spatial statistics; (B) Creation of mean and standard deviation images using all subjects; (C) Individual subjects' FA maps were used to create FA *z*-maps for each subject; (D) *z*-FA maps masked to the Johns Hopkins white matter atlas; (E) Identification of potholes by the identification of contiguous voxels that fall below a thesholded *z*-value; (F) Comparison of patients versus controls at different *z*-thresholds and minimum cluster sizes.