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Investigation into local white matter abnormality in emotional processing and sensorimotor areas using an automatically annotated fiber clustering in major depressive disorder

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ABSTRACT

This work presents an automatically annotated fiber cluster (AAFC) method to enable identification of anatomically meaningful white matter structures from the whole brain tractography. The proposed method consists of 1) a study-specific whole brain white matter parcellation using a well-established data-driven groupwise fiber clustering pipeline to segment tractography into multiple fiber clusters, and 2) a novel cluster annotation method to automatically assign an anatomical tract annotation to each fiber cluster by employing cortical parcellation information across multiple subjects. The novelty of the AAFC method is that it leverages group-wise information about the fiber clusters, including their fiber geometry and cortical terminations, to compute a tract anatomical label for each cluster in an automated fashion. We demonstrate the proposed AAFC method in an application of investigating white matter abnormality in emotional processing and sensorimotor areas in major depressive disorder (MDD). Seven tracts of interest related to emotional processing and sensorimotor functions are automatically identified using the proposed AAFC method as well as a comparable method that uses a cortical parcellation alone. Experimental results indicate that our proposed method is more consistent in identifying the tracts across subjects and across hemispheres in terms of the number of fibers. In addition, we perform a between-group statistical analysis in 31 MDD patients and 62 healthy subjects on the identified tracts using our AAFC method. We find statistical differences in diffusion measures in local regions within a fiber tract (e.g. 4 fiber clusters within the identified left hemisphere cingulum bundle (consisting of 14 clusters) are significantly different between the two groups), suggesting the ability of our method in identifying potential abnormality specific to subdivisions of a white matter structure.

Introduction

Diffusion magnetic resonance imaging (dMRI) enables detection of microstructural white matter (WM) changes in vivo (Makris et al., 1997; Pajevic and Basser, 2003; Shimony et al., 1999). dMRI tractography is a noninvasive neuroimaging technique that is able to identify WM fiber tracts in the human brain (Basser et al., 2000; Ciccarelli et al., 2008). A fiber tract is a collection of central nervous system axons having a common site of origin and a common destination (Makris et al., 1997; Noback et al., 2005). For instance, the corticospinal tract (CST) originates in the cerebral cortex and ends in the spinal cord. Important goals of tractography research are to identify brain connective structures in vivo and to measure biological properties of these structures that are sensitive to clinical abnormalities. To investigate local WM abnormalities in specific structures, tractography has been employed in quantitative analysis of scalar measures derived from the diffusion tensor, such as anisotropy or diffusivity measures (Johansen-Berg and Behrens, 2006; O'Donnell and Westin, 2011). Whole-brain tractography, however, produces an

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unstructured set of thousands of fiber trajectories by estimating the course of all connections in the entire WM, whereas clinical applications often demand targeted tracking of specific fiber tracts.

To understand such massive amounts of data, whole-brain tractography is often segmented to identify fiber tract(s) of interest. One commonly used method identifies key fiber tracts by requiring manual tracing of regions of interest (ROIs) followed by assessment of the fibers that pass through the ROIs (Mori et al., 2006). This manual identification of ROIs used to define fiber tracts is operator dependent and time-consuming (Huang et al., 2004). Moreover, manual selection methods can suffer from operator bias (Bürgel et al., 2009; Radmanesh et al., 2015; Voineskos et al., 2009). Therefore, a number of automatic tract identification strategies have been proposed, which can be generally categorized into cortical-parcellation-based (CPB) (Cloutman and Ralph, 2012; O'Donnell et al., 2013; Wassermann et al., 2016) and fiber clustering (FC) methods (Guevara et al., 2016; Moberts et al., 2005; O'Donnell et al., 2013). CPB takes into account morphological information from the cortical folding pattern, while FC considers the shape and the trajectory of the fibers once these leave the cortex.

CPB methods (O'Donnell et al., 2013; Sporns et al., 2005; Wassermann et al., 2016), e.g. the white matter query language (WMQL) (Wassermann et al., 2016), segment tractography according to a cortical parcellation, focusing on the structural connectivity between pairs of parcellated cortical/subcortical regions (Gong et al., 2008; Honey et al., 2009; Zhang et al., 2017). While this allows for highly specific identification, fibers that do not intersect the gray matter (GM) are excluded from the identification and this may hence result in a low sensitivity of tract identification (Vercruysse et al., 2014). In addition, the CPB method is dependent on the cortical parcellation of individual subjects, which could be affected by individual anatomical variations (Ashburner and Friston, 2000; Bonilha et al., 2015; Fischl et al., 2004).

Compared to CPB, FC relies on a different WM connectivity modeling assumption, aiming to group neighboring fibers with similar trajectories into clusters, which reconstruct fiber tracts according to the WM anatomy (Guevara et al., 2012; Maddah et al., 2008; O'Donnell and Westin, 2007). A variety of methods have been developed for unsupervised clustering of whole brain tractography in individual subjects based on various types of features such as geometry, anatomy, connection, or function (Garyfallidis et al., 2012; Ge et al., 2012, 2013; Guevara et al., 2011; Wassermann et al., 2010). Our work in groupwise fiber clustering (O'Donnell et al., 2012; O'Donnell and Westin, 2007) has demonstrated that white matter regions can be automatically clustered, correspond across subjects, and be augmented with anatomical annotations. Recently, we have applied the groupwise fiber clustering strategy to perform data-driven white matter parcellation, enabling whole-brain white matter analyses in groups of subjects, for example in autism (Zhang et al., 2018a), attention deficit hyperactivity disorder (Zhang et al., 2018b) and patients with brain tumors (O'Donnell et al., 2017). While both CPB and FC eliminate operator-specific intra- and inter-subject inconsistencies in tract delineation, our previous work (Zhang et al., 2017) demonstrated that FC may have a higher white matter parcellation consistency across subjects than the CPB method.

While the data-driven fiber clustering method has high consistency across subjects, it does have one drawback in interpretation of the fiber clusters. Fiber clusters obtained by unsupervised clustering need anatomical labels to identify anatomically meaningful white matter structures. Unlike the connections defined by a CPB method that are easily interpreted because their cortical terminations are known, in the FC approach this interpretation requires additional expert analyses to identify anatomically meaningful tracts by manually assigning an anatomical annotation to each fiber cluster (Guevara et al., 2012; O'Donnell and Westin, 2007). The combination of the two methods, representing a hybrid strategy, has been suggested to have advantages over their individual usages (Xia et al., 2005; Li et al., 2010; Ros et al., 2013; Wassermann et al., 2016; Ge et al., 2012; Siless et al., 2018; Tunç et al., 2013; Wang et al., 2013a; Guevara et al., 2017; Román et al., 2017).

In this study, we propose a hybrid white matter atlasing approach by combining CPB and FC strategies for automatic anatomical annotation of fiber clusters, which we refer to as the automatically annotated fiber clustering (AAFC) method. The goal of the proposed method is to provide an automated pipeline to perform white matter parcellation to identify anatomical fiber tracts. While FC provides a data-driven groupwise fiber clustering for fine parcellation according to white matter anatomy, CPB allows us to define anatomical annotations (such as the corticospinal tract (CST)) of fiber clusters. The combination of the two strategies allows the anatomical annotation of fiber tracts by including both brain GM and WM anatomy into the analysis. The benefits of the AAFC method are that: 1) it provides an automatic anatomical tract annotation pipeline to create study-specific white matter parcellations without using any expert annotation of fiber tracts, 2) it derives a high consistency of the identified fiber tracts across multiple subjects and across hemispheres, and 3) it allows investigation of local regions of certain fiber tracts (e.g. we obtained 7 subdivisions of the CST tract).

We demonstrate the proposed method in an application to analyze between-group white matter tract differences in a dataset including major depressive disorder (MDD) and healthy control (HC) groups. MDD is a common psychiatric disorder that is characterized by cognitive deficits and affective symptoms. Research studies have recognized MDD as a disconnection problem that involves many neural connections between brain functional regions (Cheng et al., 2016; Fu et al., 2015; Gong and He, 2015; Korgaonkar et al., 2014; Kostic et al., 2016; Liao et al., 2013). An increasing number of neuroimaging studies have focused on emotion regulation and have consistently shown that emotion dysregulation is one of the central features and underlying mechanisms of MDD. In particular, dMRI studies have suggested that there could be white matter abnormalities in emotional processing and sensorimotor areas in MDD (Delvecchio et al., 2012; Lu et al., 2016; Rizk et al., 2017; Smith and Bulman-Fleming, 2005; Tucker et al., 1999; Tymofiyeva et al., 2017; Zhang et al., 2011). Therefore, in this study, we apply our AAFC method to automatically identify the fiber tracts that are related to these brain functional areas and investigate potential white matter group differences specific to local regions of these tracts. We hypothesize that our method can reveal white matter changes within subdivisions of the fiber tracts, as defined by fiber clustering. A between-group (MDD vs HC) difference analysis is performed by comparing fractional anisotropy (FA) and mean diffusivity (MD) measured from each identified fiber tract and each fiber cluster of the fiber tract. To our knowledge this work represents the first automatic anatomical tract annotation method applied to investigate local white matter abnormality in MDD.

Materials and methods

Overview

The proposed AAFC method has four main steps (Fig. 1): whole brain tractography, study-specific data-driven groupwise fiber clustering, parcellation-based cluster identification, and automatic tract annotation across subjects. The purpose of these steps is to identify common white matter structures (fiber clusters) in the population and then to assign the fiber clusters to anatomically known white matter tracts according to the anatomical definitions that are predefined in the white matter query language (WMQL) (Wassermann et al., 2016).

Data acquisition and processing

Participants and MRI acquisition

The study requested access to data collected at the Department of Psychiatry at the Affiliated Brain Hospital of Guangzhou Medical University for the purpose of scientific investigation. Demographic information and results of between-group comparisons are shown in Table 1. A total of 93 subjects were studied, including 31 medication-free MDD patients and 62 healthy controls. All subjects were right-handed and of