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Investigating connectivity between the cerebellum and thalamus in schizophrenia using diffusion tensor tractography: A pilot study

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Abstract

Connections of the cortical–thalamic–cerebellar–cortical regions provide a framework for studying the neural substrates of schizophrenia. A novel diffusion tensor tractography method was used to evaluate the differences in white matter connectivity between 12 patients with schizophrenia and 10 controls. For the tract tracing, we focused on the connection between the cerebellum and the thalamus. Fractional anisotropy (FA) measures along the fiber tracks were compared between patients and the control sample. Fiber tracts located between the cerebellar white matter and the thalamus exhibit a reduced FA in patients with schizophrenia in comparison with controls. The FA values along the defined fiber tracts were not overall reduced but exhibited a reduction in the anisotropy in the region in the superior cerebellar peduncles projecting towards the red nucleus.

Keywords

Diffusion tensor; Schizophrenia; Tractography

1. Introduction

Despite compelling evidence for a variety of neurobiologic abnormalities in schizophrenia, the precise nature of the pathogenesis underlying the disease has remained elusive. This may be a consequence of the heterogeneous nature of its symptoms, ranging from subtle attenuations in effect to overt hallucinations or disorganization of thought. Remarkably, current techniques have led to a state of knowledge that is only modestly more advanced than some of the original hypotheses of a century ago. In 1906, Wernicke proposed that the basic cause of schizophrenia may be a disruption in the network of neurons and neural fibers connecting the various regions of the brain (Wernicke, 1906). Until recently, the only way to test his hypothesis was to dissect the postmortem brains of individuals with schizophrenia. While this may yield valuable findings, there are significant limitations in postmortem work

given the confounding influences of advanced age and/or conditions of death as well as the obvious inability to collect any concurrent behavioral data. Modern imaging modalities have opened up the living brain in a way that may permit an *in vivo* assessment of Wernicke's hypothesis. In particular, magnetic resonance imaging (MRI) has been used extensively to study brain structure in patients with schizophrenia. In structural imaging, the white matter in the brain has typically been classified as a single compartment. This approach permits a volumetric assessment, but it does not necessarily provide information regarding specific neural circuits or their connectivity.

Recently, diffusion tensor imaging (DTI) has emerged as an effective modality for investigating the microstructure of fibrous tissues such as cerebral white matter that are critical to assessment of neural connectivity. Thus far, DTI studies on schizophrenia have provided substantial evidence for Wernicke's hypothesis. Individuals with schizophrenia exhibit widespread white matter diffusion deficits (Lim et al., 1999; Agartz et al., 2001; Minami et al., 2003). Specific regions of the brain that have been identified as being abnormal include the prefrontal cortex (Buchsbaum et al., 1998), the corpus callosum splenium but not the genu (Foong et al., 2000; Agartz et al., 2001), the anterior cingulum (Wang et al., 2004), the cingulum bundle (Kubicki et al., 2003; Sun et al., 2003), the left uncinate fasciculus and the left arcuate fasciculus (Burns et al., 2003). A lack of uncinate fasciculus left-greater-than-right asymmetry in anisotropic diffusion (Kubicki et al., 2002) has also been found. Finally, regions of the arcuate fasciculus and anterior corpus callosum have been implicated as potentially involved in the development of auditory hallucinations (Hubl et al., 2004). Many of these studies have focused primarily on frontotemporal and frontoparietal white matter fiber tracts. One limitation of studies utilizing atlas-based regions of interest for FA measurements is the difficulty in removing variability due in shape differences between groups. This limitation may be overcome using diffusion tensor tractography to identify corresponding regions.

Historically, the cerebellum has rarely been a region of interest in the study of schizophrenia. Recent evidence has shown, however, that disruptions in the cortical–thalamic–cerebellar–cortical circuit (CCTCC) may represent a key abnormality that underlies the clinical manifestations of the illness. The disruption in the interplay between these brain regions has been referred to as “cognitive dysmetria,” a potentially fundamental deficit in the pathology of schizophrenia (Andreasen et al., 1998; Andreasen, 1999; Schmahmann, 2004). While other regions of the cortical–thalamic–cerebellar–cortical circuit have been more thoroughly studied, it has not yet been evaluated whether the white matter fiber tracts connecting the cerebellum and the thalamus may exhibit the same kind of reduction in integrity that has been found in other cerebral regions in individuals with schizophrenia.

In this study, DTI and a novel fiber tracking algorithm called GTRACT (Guided Tensor Restore Anatomical Connectivity Tractography) were used to test the hypothesis that individuals with schizophrenia may have reduced anisotropic diffusion in the connectivity between the cerebellum and thalamus. GTRACT was developed to solve the fiber-crossing problem that has plagued previous tractography algorithms (Cheng et al., 2006). Specifically, the focus of this work was to test the hypothesis that anisotropy of the white matter fiber tracts joining the cerebellum and the thalamus would have reduced anisotropy. This reduction in anisotropy would reflect a disorganization of the white matter within this fiber tract.

2. Methods

Subjects were imaged at the University of Iowa and the University of New Mexico after informed consent was obtained in accordance with the Institutional Review Boards at these institutions. Twelve male patients with a DSM-IV diagnosis of schizophrenia (mean age 32 ± 9.5 years) and 10 normal controls (5 males and 5 females, age 43.5 ± 9.0 years) were recruited into this study. All subjects were right or mixed handed as assessed using the Edinburgh Handedness Inventory. The patients had a mean duration of illness of 11.75 years and were all receiving atypical antipsychotic medication at the time of imaging. All control subjects were free of any other major psychiatric illness. Exclusion criteria for all subjects included head trauma, substance abuse, or medical or neurologic illness that might affect imaging measures.

MR imaging was performed on either a Siemens Symphony or Sonata 1.5 T scanner. The subjects were imaged using an imaging protocol to acquire structural MR and diffusion tensor images. The structural imaging protocol acquired multimodal scans consisting of T1 and T2 weighted sequences. The T1 sequence obtained images in the coronal plane using a 3D FLASH sequence with RF spoiling and the following parameters: TE = 6 ms, TR = 20 ms, flip angle = 30° , FOV = $160 \times 160 \times 192$ mm, matrix = $256 \times 256 \times 128$, NEX=2. The T2 images were acquired using a 2D turbo spin-echo sequence in the coronal plane with the following parameters: TE=85 ms, TR=4800 ms, slice thickness/gap = 1.8/0.0 mm, FOV = 160×160 mm, matrix = 256×256 , NEX = 3, number of echoes = 8, number of slices=124. Diffusion tensor images were obtained with the following protocol: TE=80 ms, TR = 9500 ms, flip angle = 90° , FOV = 256×256 , Matrix = 128×128 , slice thickness = 2.0 mm, slice gap = 0.2 mm, number of slices = 65, NEX = 4, B value=1000 s/mm², bandwidth=1346 Hz/pixel, number of diffusion directions =6. A second acquisition of the diffusion-weighted images was acquired within a 24-h interval.

The structural MR scans were analyzed using the BRAINS software (Andreasen et al., 1992; Andreasen et al., 1993; Magnotta et al., 2002). A standard image analysis pipeline was utilized that included the following steps: 1) spatial alignment of the T1 weighted scan along the AC–PC line and the interhemispheric fissure; 2) co-registration of the T2 images to the spatially aligned T1 (Woods et al., 1998); 3) tissue classification (Harris et al., 1999); 4) brain extraction (Magnotta et al., 1999); and 5) neural network regional brain labeling (Magnotta et al., 1999). The neural network defined regions of interest for the thalamus (Spinks et al., 2002) and the cerebellar white matter (corpus medullary) (Pierson et al., 2002) were verified by an expert anatomical rater and manually edited if required.

The diffusion-weighted images were co-registered to the $B=0$ image using a mutual information affine registration (Viola and Wells, 1995) to eliminate the effects of motion. A $3 \times 3 \times 3$ voxel neighborhood median filter was applied to the diffusion-weighted images, and then the tensor field was calculated using a background suppression threshold of 100 on the $B=0$ image. The resulting tensor image was resampled into $2 \times 2 \times 2$ mm isotropic voxel size. A fractional anisotropy (FA) image was then calculated. The $B=0$ image from the DTI series was co-registered to the AC–PC aligned T1 image using the same mutual information registration algorithm used for motion correction of the diffusion tensor images. This registration was then inverted to place the thalamus and cerebellar regions of interest into the acquisition space of the diffusion tensor images. For the tract tracing, we focused on one major pathway, which represents the connection between the cerebellum and the thalamus. The automatically segmented regions of interest defining the thalamus and cerebellar white matter on the anatomical images using the neural network brain labeling served as starting and ending regions for fiber tracking with the GTRACT software.

The algorithms used by the GTRACT software are described in detail by Cheng et al. (2006), and the reader is referred to this article for a detailed description of this algorithm. The algorithm is a two pass approach to fiber tracking. The first pass generates an approximation to the fiber tracks, and in the second pass, this information is used to guide the fiber tracking when the fiber tracking enters ambiguous regions (defined as large curvature or low anisotropy regions). The GTRACT method simulates the branching behavior of the fiber bundles and has been shown previously to be less sensitive to noise as compared with standard streamline-based methods (Magnotta and Cheng, 2005). The GTRACT algorithm has four steps: 1) forward and backward tracking, 2) merging, 3) generation of mean fiber position, and 4) guided tracking. This tracking method requires two pre-defined regions: a starting and ending region. Therefore, some prior knowledge about the underlying white matter structure is required, and anatomical regions of interest for the starting and ending regions need to be defined.

The GTRACT algorithm was applied on these datasets using the following parameters: seed threshold=0.28, tracking threshold=0.22, step size=1 voxel (2 mm), maximum branching points=5, branching anisotropy threshold=0.26, branching curvature threshold=45°, maximum length=80 mm, guided tracking curvature threshold=15°. Since the fiber tracking is being seeded by the cerebellar white matter, a relatively high seed threshold can be used to initiate fiber tracking.

Once the fiber tracts were generated, they were converted from a 3D representation to a 2D representation. This process treats the fiber tract as a rubber band that is anchored at both ends. The length of the fiber tracts was normalized allowing the overall tracts to shrink or expand. The fiber tracts were divided into 100 segments. Between-group comparisons of FA values along the generated fiber tracts were performed using the *R* statistical language (v2.2.0). *T*-tests were performed to compare the patients with the normal controls at each of the 100 points along the path assuming unequal variance. This analysis was performed separately for each tract and time point. A *P*-value of 0.05 was accepted for significant difference between groups. The QVALUE library for *R* was utilized to access the false discovery rate of the accepted *P*-values (Storey, 2002; Storey and Tibshirani, 2003). The *q*-values define the probability of a false positive within the accepted *P*-values.

While the reliability of the GTRACT was previously addressed (Cheng et al., 2006), correlation coefficients between the two imaging sessions were determined to estimate the reliability of the fiber tracking algorithm within this sample. Correlation coefficients were estimated by taking the fiber tracks after resampling into the space of the anatomical images and correlating the FA values along the fiber tracts between the two imaging sessions in a subject. The correlation coefficients were averaged to get an estimate of the reliability for each group and side.

3. Results

Correlation coefficients of the FA values along the fiber tracts in the control subjects were 0.94 and 0.95 for the left cerebellum to right thalamus and right cerebellum to left thalamus, respectively. The patients with schizophrenia had lower correlation coefficients of 0.87 and 0.88. Even with the high degree of reliability between the two time points, analysis for the two measurements was carried out independently.

Due to the differences in age and gender composition between the controls and the patients, we first investigated what effect these variables had on the generated fiber tracts. Statistically significant differences in the FA values along the identified fiber tracts between males and females in the control sample were determined. A *t*-test comparing male to female

participants for each point along the tract was computed, but no statistically significant regional differences were found. To test whether age differences may affect these results, FA values at each point along the fiber tract were correlated (Pearson's Product Moment correlation) with the subject's age for the entire sample (patients and controls). One of the measurements, right cerebellum to left thalamus, showed an area of significant correlation with age (points 55–74 along the path). This was not replicated in the first measurement, and no significant correlations with age ($P < 0.05$) were found for the contralateral tracts.

For the fiber tracts connecting the left cerebellum to the right thalamus, the patients with schizophrenia had a significant reduction ($P < 0.05$) in FA values along the fiber tracts between points 40 and 70 (Fig. 1a–b). Most of this region was from the superior cerebellar peduncles projecting towards the red nucleus (Fig. 2). This difference in FA values between the patients and controls was similar in both the test and retest measurements. A false discovery rate (FDR) analysis was performed using the P -values obtained along the tract between the patients and controls. The FDR analysis reported q -values of 0.35 and 0.12 for the time 1 and time 2 measurements, respectively. For the tracts between the right cerebellum and the left thalamus, a significant reduction ($P < 0.05$) in the FA values for the patients (points 52–65) was found in the first measurement, but only showed a trend for the second measurement (Fig. 1c–d). The false discovery rate q -value for the first measurement was 0.18. This region is very similar to the contralateral fiber tracts as shown in Fig. 2. None of these comparisons would be significant using Bonferroni correction. The data presented here suggest that the connectivity between the cerebellum and thalamus is not reduced over the entire tract, but may reflect discrete regions where deficits exist between these regions.

4. Discussion

The primary finding of this study was that the fiber tracts located between the cerebellar white matter and the thalamus exhibit a reduced FA in patients with schizophrenia in comparison to normal controls. The FA values along the defined fiber tracts were not reduced along the entire length of the tract, but exhibited a reduction in the anisotropy in the region of the superior cerebellar peduncles projecting towards the red nucleus. These findings were significant for both replications of data for the left cerebellum to right thalamus tract. For the right cerebellum to left thalamus, one replication was significant while the other exhibited a similar trend. Of note, the FA differences found on each side occurred in roughly the same position along the fiber tracts. The region of the superior cerebellar peduncle or brachium conjunctivum serves as the decussation of the cerebellar fibers projecting from the cerebellum to the red nucleus and onto the thalamus. Typically, this area on diffusion-weighted imaging appears as a bright region reflecting a reduction in water mobility due to the densely packed fibers within this region. Therefore, it is possible that methods comparing diffusion tensor scalar values within this region may have greater power since fibers from both cerebellar hemispheres are crossing within this region projecting to the cerebrum. Greater exploration of these findings may help delineate the thalamic–cerebellar circuitry that may be important to an understanding of abnormal neural pathways in schizophrenia.

There are several limitations to the interpretation of these results. The sample used in this study was small, it was not well matched for males and females, and the controls were significantly older than the patient population. The results will need to be confirmed in a larger, better matched cohort. Even though these limitations exist within the sample, data for a scan/rescan evaluation of the method were available. Based on the correlation of the FA values along the fiber tracts, the GTRACT fiber-tracking algorithm is able to produce similar connectivity indexes between scans. A previous evaluation of the algorithm also showed that the mean fiber position between two scanning sessions was on the order of a

voxel (2 mm). These findings suggest an abnormality in the connectivity between the cerebellum and thalamus exists in schizophrenia. However, an overall reduction in the FA values cannot be ruled out given the potential for greater signal variation within the superior cerebellar peduncles due to the densely packed fibers within this region. In order to more fully understand the role of the cortical–thalamic–cerebellar–cortical network abnormalities in schizophrenia, further research must be done, including an analysis of the other regions of this particular circuit. While the primary focus of this article was on these two tracts, it is important to extend analyses to additional fiber tracts connecting other brain regions based on positive findings in the schizophrenia literature.

Recent research has suggested that cognitive dysmetria, a dysfunction in managing and performing information-processing tasks, could potentially explain many of schizophrenia's symptoms (Andreasen et al., 1996). Both the cerebellum and thalamus along the CCTCC have been implicated as contributing to cognitive dysmetria in persons with schizophrenia (Andreasen et al., 1996; Andreasen, 1997; Andreasen et al., 1998). Specifically, the middle cerebellar peduncle has been shown to have a decreased FA in schizophrenic patients (Okugawa et al., 2005; Okugawa et al., 2006), although a previous study had reported that there was no significant difference in FA in the superior and middle cerebellar peduncles of schizophrenic patients (Wang et al., 2003). The results suggest that there may indeed be reduced FA along the cerebellum–thalamus region of the CCTCC. Specific regions along this tract were shown to exhibit significant differences between schizophrenic patients and controls. At the least, this study suggests that the connectivity between the nodes of the CCTCC warrants more attention with reference to its contribution to schizophrenia. These results support the assertion that schizophrenia should no longer be thought of as a disease of one brain region, but rather more generally as a disease of cognition and connectivity (Andreasen et al., 1996; Lim et al., 1999) and that diffusion tensor tractography has utility in the study of psychiatric disorders.

In order to more fully understand the role of the cortical–thalamic–cerebellar–cortical network abnormalities in schizophrenia, further research must be done including an analysis of the other regions of this particular circuit. Also, these methods should be repeated on a larger group of patients and controls to confirm their reliability. While it is impossible to infer from diffusion tensor imaging the underlying reason for the reduction in anisotropy along the fiber tract, it reflects some disorganization in the underlying fiber architecture. These changes may represent a pathologic process resulting in the development of schizophrenia.

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Fig. 1.

FA values along the tracts connecting the cerebellum and thalamus. The graphs show the fractional anisotropy (FA) with the error bars representing the standard deviation. The P -values at each of the tract locations are displayed in green with the significance level of $P < 0.05$ marked as a solid line. The fiber tracts from the left cerebellum to right thalamus are shown in a and b while the right cerebellum to left thalamus are shown in c and d. The black box defines locations along the fiber tract that fall below $P < 0.05$.

Fig. 2.

The top row shows the fiber tracts between the left cerebellum and right thalamus for one of the subjects shown in axial and coronal orientations. The bottom row shows the fiber tracts between the right cerebellum and left thalamus. The fiber tracts are color-coded, showing the area of significant reduction in the FA values in patients with schizophrenia in blue and the remaining areas in red.