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The role of modern imaging modalities on deep brain stimulation targeting for mental illness

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Summary

Introduction. The reversible nature of deep brain stimulation (DBS) brought renewed interest on surgery to medically intractable mental illnesses. The explosion of anatomical and functional imaging has allowed the development of new potential targets and the understanding of historical targets.

Methods. Fifteen patients undergoing stereotactic surgery for movement disorders, at UCLAs interventional MRI operating-room, were studied with fiber tracking. Stereotactic targets and fiber tracking were determined on MRIs using the Schaltenbrand-Wahren atlas for definition in the iPlan software. Cingulate, subcaudate, BA25/CgWM, amygdala, posterior hypothalamus, orbitofrontal cortex, nucleus accumbens, anterior limb of the internal capsule and dorsomedial thalamus were studied. DTI parameters used ranged from 10 to 20 mm for voxel size in the x/y/z planes, fiber length was kept constant at 36 mm, and fractional anisotropy (FA) threshold varied from 0.20 to 0.25.

Results. Reliable interconnectivity of targets were determined with DTI and related to PET imaging. Mental illness targets were observed with functional and fiber tract maps. This confirmation yields reliability to DTI imaging in order to determine novel targets and enhance the understanding of areas not well understood.

Conclusions. Currently available imaging techniques, the reversibility of DBS to modulate targets promises to bring a brighter future for surgery of mental illness.

Keywords: DTI; MRI; OCD; depression; diffusion tractography; mental illness; PET; psychosurgery.

Introduction

Since the beginning of psychosurgery applications in humans in the 1930s, there has been controversy [18]. Although Egas Moniz was suggested to be nominated for the 1944 Nobel Prize by Walter Freeman for "his fundamental contribution to the surgical treatment of functional mental disorders," little understanding was known regarding mental illness [18]. By the 1950s, stereotactic surgery for movement disorders became commonplace along with several psychosurgery applications [23]. Ablative techniques were abandoned for behavior surgery following the controversies of psychosurgery. Deep brain stimulation brings new hope for behavior surgery as it is reversible and adjustable. Furthermore, the knowledge and fundamental understanding of the brain has rekindled hopes for treating mental illness refractory to medical therapy.

Functional imaging modalities, such as PET and fMRI have demonstrated various abnormalities in obsessive-compulsive disorder, major depression, Tourette syndrome, cluster headache, and numerous other disorders. As these modalities have added to our understanding of disease states, understanding fundamental brain interconnectivity will greatly enhance our interpretation and ultimate understanding of the brain in its disease states.

The application of Diffusion Tensor Magnetic Resonance Imaging has enhanced the ability to view anatomical detail beyond what is seen by conventional MRI or CT scans. This diffusion tensor imaging (DTI) observes the net diffusion of water along fiber tracts allowing visualization of their orientation in space [4]. Because of this fractional anisotropy (FA), visualization along unimpeded fibers tracts is optimal, but the resolution of intersecting bands of fibers is limited. Despite this clear limitation to the technique, DTI imaging has greatly surpassed any other immediately available imaging modality with regards to the anatomical visualization of fiber tracts *in vivo*.

In this preliminary study, we sought to identify major fiber tract bundles by DTI as they relate to the anterior

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cingulate gyrus, nucleus accumbens, subcaudate region, BA25/CgWM, amygdala, posterior hypothalamus, inferior thalamic peduncle, anterior limb of the internal capsule, and dorsomedial thalamus. These targets have both historical significance as well as modern implications for deep brain stimulation and neurosurgical interventions.

Materials and methods

After institutional review board (IRB) approval, we retrospectively reviewed 15 MRIs of patients who underwent DBS for movement disorders (Table 1). These patients had DTI imaging pre-operatively performed in 1.5 Tesla Sonata intraoperative MRI (iMRI) suite at UCLA Medical Center. Fiber tracking acquisition was undertaken before placement of the leksell stereotactic frame, placed parallel to Reid's line under propofol sedation. A detailed description of the stereotactic procedure as well as the imaging acquisition for targeting has been previously reported. [5, 12].

Anterior cingulate, nucleus accumbens, subcaudate region, BA25/CgWM, amygdala, posterior hypothalamus, inferior thalamic peduncle, anterior limb of the internal capsule, and dorsomedial thalamus targets were identified by stereotactic coordinate targeting utilizing the Schaltenbrand-Wahren atlas for definition and confirmation in the iPlan software (BrainLab, Heimstetten, Germany). Volume of interest (VOI) was defined at the region of interest (ROI) along the factitious trajectory for DBS planning. Fiber tractography was performed at each seed point in the VOI. DTI parameters used ranged from 10 to 20 mm for voxel size in the x, y and z-plane, minimal fiber length was kept constant at 36 mm, and fractional anisotropy (FA) threshold varied from 0.20 to 0.25.

Table 1. *Demographic characteristics of the patients with DTI MRI analyzed for mental illness targets. PD, Parkinson disease; CP, Cerebral Palsy; STN, Subthalamic Nucleus; GPi, Globus Pallidus Internus*

Diagnosis	Age	Sex	Target
PD	79	M	STN bilaterally
PD	62	F	GPi bilaterally
PD	75	M	STN bilaterally
PD	66	M	STN (right)
PD	71	F	STN (left)
CP with dystonia	15	F	GPi bilaterally
CP with dystonia	21	F	GPi bilaterally
PD	45	M	STN bilaterally
PD	55	F	STN bilaterally
CP with choreoathetosis	29	F	GPi bilaterally
PD	52	M	STN bilaterally
PD	45	M	STN bilaterally
PD	48	F	GPi bilaterally
PD	61	M	STN bilaterally
PD	54	M	STN bilaterally

Results

Anterior cingulate coordinates calculated to 7 mm lateral to midline and 20 mm caudal to the tip of frontal horns of the lateral ventricle and 29 mm dorsal to the AC–PC plane located in the center of the cingulate gyrus white matter. DTI imaging at this target demonstrated fibers in the cingulate fasciculus as well as fibers directed towards prefrontal regions. Fibers of the corpus callosum were in close proximity and also incorporated (Fig. 1).

Nucleus accumbens coordinates calculated to 7 mm lateral to midline, 4 mm ventral to AC–PC plane, and 1.5 mm rostral to anterior edge of anterior commissure. DTI imaging at this target demonstrated several groups of fiber bundles directed towards orbitofrontal/prefrontal areas, via uncinate fasciculus to temporal lobe, towards tegmentum of midbrain/pons, the fornix, and the inferior occipito-frontal fasciculus (Fig. 2).

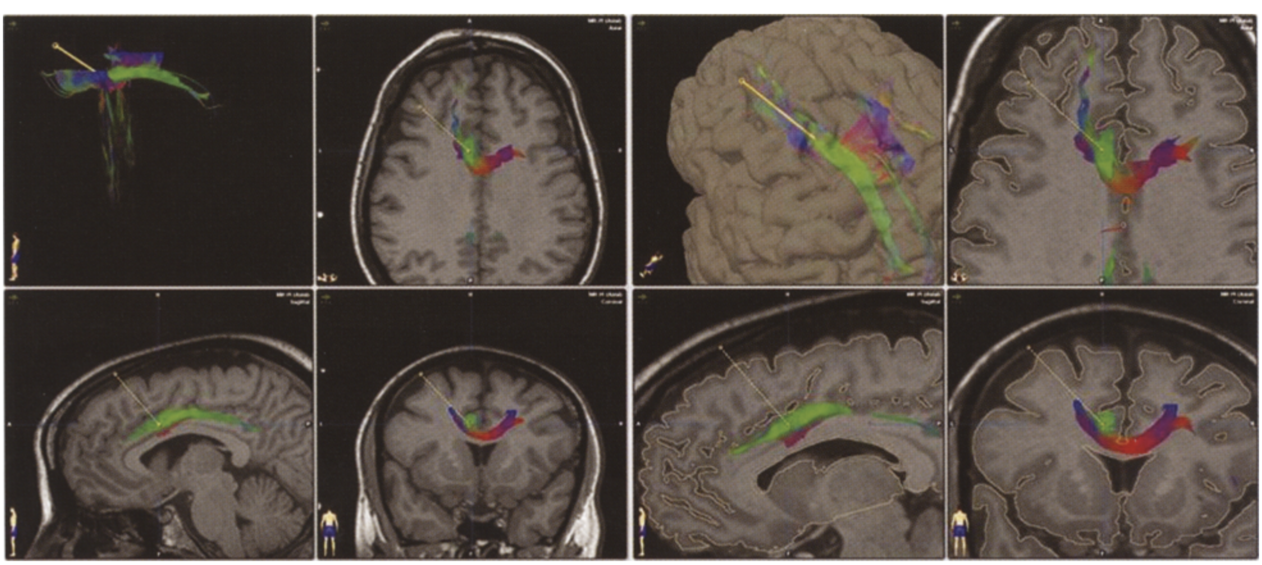

Fig. 1. DTI processing at anterior cingulate target. Fibers are seen in the cingulate fasciculus as well as fibers directed towards prefrontal regions

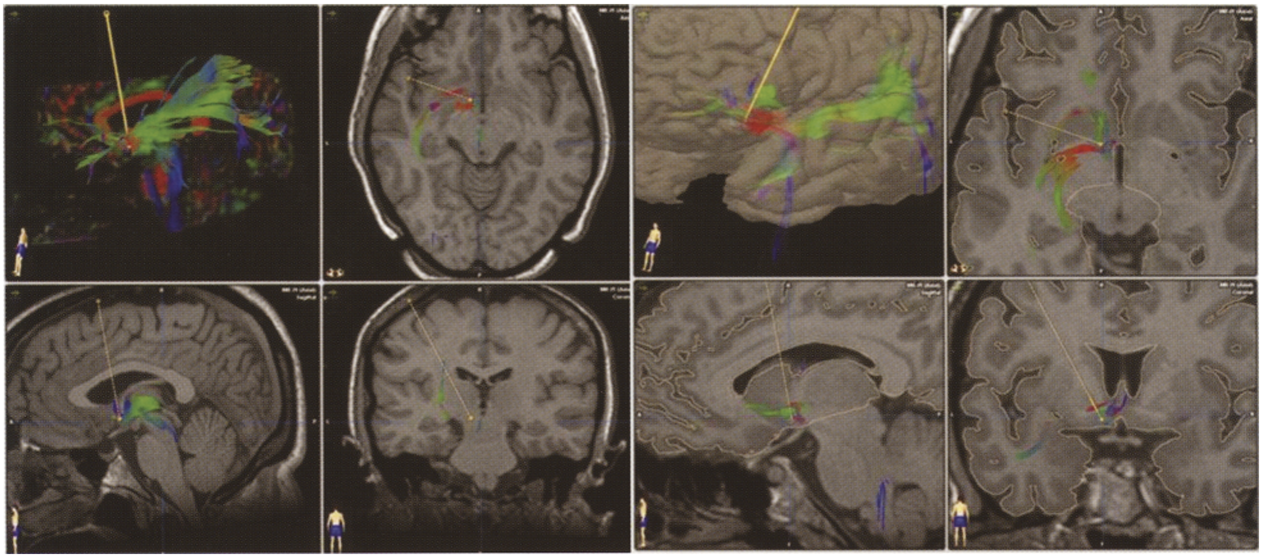

Fig. 2. DTI processing at nucleus accumbens. Fiber tracts can be seen directed towards orbitofrontal region, brainstem tegmentum, temporal lobe, the fornix, and through the inferior occipito-frontal fasciculus

Subcaudate region coordinates calculated to 15 mm lateral to midline and 11 mm above the planum sphenoidale at the most anterior part of the sella turcica. This was 19 mm anterior to the anterior commissure, 15.5 mm lateral to midline, and 10.5 mm ventral to AC–PC plane. DTI fibers could be seen directed towards orbitofrontal areas and posteriorly through the inferior occipito-frontal fasciculus.

BA25/CgWM coordinates calculated to 6 mm lateral to midline, 2 mm ventral to AC–PC plane, and was 3 mm caudal to the tip of the frontal horn. This was 24 mm anterior to anterior commissure, 6 mm lateral to midline, and 2 mm ventral to AC–PC plane. DTI imaging revealed fibers directed towards orbitofrontal/prefrontal regions as well as to cingulate fasciculus (Fig. 3).

Posterior hypothalamus coordinates calculated to 3 mm lateral to midline, 3 mm rostral to midcommissural point, and 5 mm ventral to AC–PC plane. DTI map shows numerous connections. Namely, projections into orbitofrontal regions, prefrontal regions, fornix, and tegmentum of brainstem could be seen.

Inferior thalamic peduncle coordinates calculated to 8 mm caudal to the anterior commissure, 6 mm lateral to midline, and at the level of the AC–PC plane. DTI

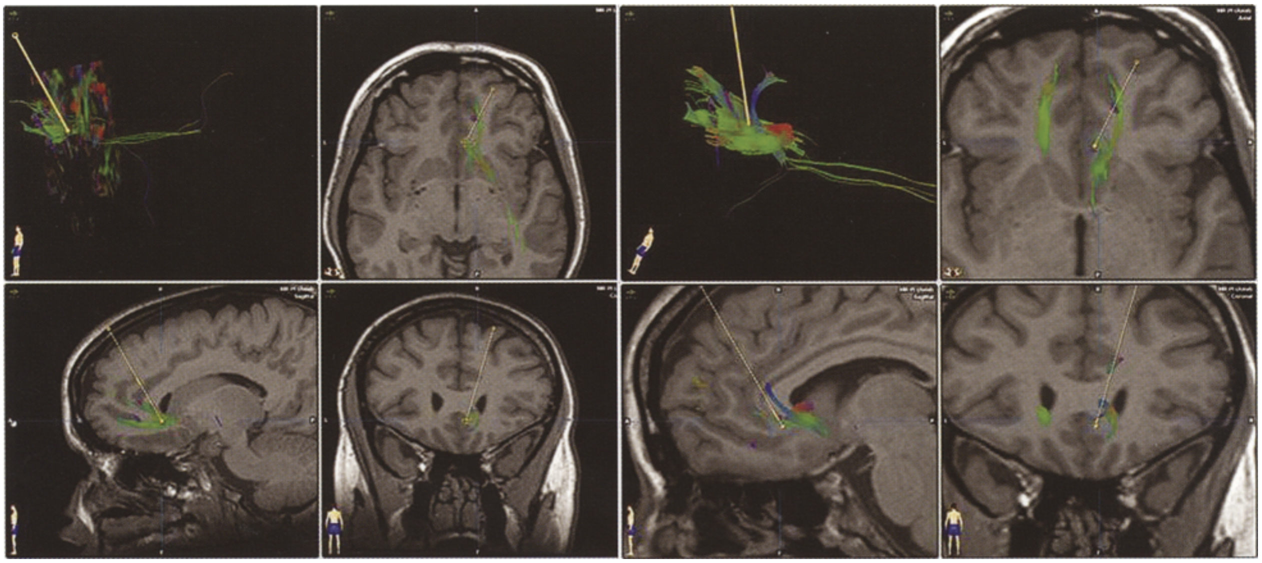

Fig. 3. DTI imaging at BA25/CgWM. Fibers can be seen directed towards prefrontal and orbitofrontal regions as well as to the anterior cingulate

imaging showed connections to thalamus, tegmentum of brainstem, and prefrontal regions. Anterior limb of the internal capsule coordinates calculated to 20 mm lateral to midline, 7 mm caudal from the tip of the frontal horn, and was at the level of the AC–PC plane. Fiber bundles were observed projecting towards orbitofrontal and prefrontal regions, via uncinate fasciculus to temporal lobe, as well as to parietal and occipital lobes.

Dorsomedial thalamus coordinates calculated to 5.8 mm lateral to midline, 14.8 mm dorsal to the AC–PC line at the midcommissural point. DTI imaging showed heavy fiber bundles directed towards the prefrontal region through the superior thalamic peduncle. The fornix was also in close proximity and fibers could be seen heading to the temporal lobe.

Coordinates for the amygdala were 18.8 mm lateral to midline, 14 mm ventral to AC–PC plane, and 1 mm caudal to the anterior commissure. When the amygdala was targeted, the DTI map showed fibers projecting through the uncinate fasciculus to the hypothalamic and septal regions as well as fibers passing through the tegmentum of the brainstem. The region of the inferior occipito-frontal fasciculus was incorporated and also the optic radiations. Coordinates for the hippocampus were 18 mm lateral to midline, 17 mm ventral to AC–PC plane, and 7 mm posterior to anterior commissure. When the hippocampus was targeted, the DTI maps showed fibers projecting through the fornices. In addition, the uncinate fasciculus was also seen as well as fibers of the optic radiations and the inferior occipito-frontal fasciculus. There were many fiber tracts overlapping between the amygdala and hippocampal targets.

Discussion

As the demand for neurosurgical treatment of mental illnesses continues to rise, enhanced anatomical and functional imaging will be required to match this demand. DTI imaging clearly enhances our interpretation of functional imaging, providing new insights, understanding, and targets that may be utilized for the treatment of various diseases.

We explored many of the regional connections both within and surrounding critical structures involved in mental illness with DTI imaging. Clearly, regions known to be involved in mental illness were identified and fibers emanating from these regions, projecting to other brain structures involved with mental illness were visualized. For example, many of the connections we found between the amygdala and hippocampus regions are similar to results found in the literature [21]. Hippocampal and amygdaloid interactions with nucleus accumbens have been well identified [9]. In our DTI analysis, we could see that the closest fiber tract emanating from that region was contained in the uncinate fasciculus.

DTI images of the uncinate fasciculus, inferior occipito-frontal fasciculus, and optic radiations seen in our study coincides with other DTI studies [10]. In addition, many of the prefrontal and orbitofrontal connections seen has marked agreement with known frontal lobe anatomy [24]. The prefrontal cortex has numerous parallel circuits and mediate diverse behaviors and emotions [3]. The prefrontal region in our study demonstrated numerous connections and tracts in relation to the anterior cingulate gyrus, nucleus accumbens, anterior limb of the internal capsule, dorsomedial thalamus, posterior hypothalamus, and BA25/CgWM.

There has been a boost of neuroimaging studies attempting to define anatomical and/or functional patterns of abnormalities correlating to defined psychiatric disorders. Many of the evidences are not clear cut. It is not uncommon that opposite findings are reported by different studies in regards to volumetric changes in brain structures [6, 17, 19, 26] and PET findings [1, 2]. These new imaging modalities allowed however substantial advance in neuroanatomical and functional knowledge about intrinsic abnormalities specific linked to the major psychiatric disorders [27]. For instance, functional disruption of the normal dopaminergic innervation involving the caudate, putamen, amygdala, midbrain and ventral striatum in schizophrenic patients has been consistently reported in the literature [13, 15, 16]. Synthesis and dopamine turnover was elevated about 20% in the caudate and the putamen and about 50% in the amygdala and the midbrain of patients with schizophrenia [11]. borderline personality disorder, characterized by uncontrolled anger often leading to aggressiveness, showed consistent hypoactivation of the pre-frontal cortex (PFC) and ventral amygdala circuitry mediated by serotonin[17] [20]. In fact it appears to be a disconnection between ventral amygdala and Brodmann areas 11, 12 and 47 in the PFC on the right side of borderline personality disorder patients [17]. This circuitry is well known to be involved in anger response and handling of negative emotions [7, 8, 22]. Obsessive compulsive disorder patients presented hyperactivity at the medial and ventral frontal cortex encompassing anterior cingulated area and basal ganglia with evidence of decreased NAA concentrations in the anterior cingulated area [25]. Major depression patients consistently have shown increased cerebral blood flow (CBF) measured by PET in the subgenual cingulate area (BA 25) and decreased metabolic activity in the pre-frontal cortex (BA 9/46), premotor (BA6), dorsal anterior cingulate (BA 24) and anterior insula [14].

The areas described as relevant to define a disease pattern were evaluated in our study and we were able to confirm the identification of these pathways in patients with normal anatomy and function, which is an important step validating the DTI modality for patients with mental disorders. In this preliminary study using DTI imaging to embrace various fiber territories, we can further understand the implications of mental illness targeting for deep brain stimulation. Clearly, a comprehensive anatomical and functional analysis is beyond the scope of this article. Tracts in direct connection to, or in close association with, various targets can be identified. Furthermore, as our knowledge of deep brain stimulation and mental illnesses grows other targets, such as fiber bundles, may be identified and utilized.

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