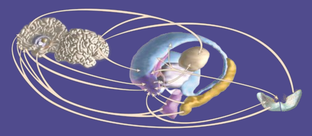

Mapping the Prefrontal Connectivity in the Internal Capsule Implication for Deep Brain Stimulation and Neuroimaging

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Introduction

The internal capsule (IC) connects prefrontal reward and executive function areas with thalamic and subcortical regions. IC abnormalities, in both volume and fractional anisotropy (FA), are associated with several psychiatric disorders, including schizophrenia, obsessive-compulsive disorder (OCD), depression, and drug addiction. Thus, the IC is of substantial interest for neuroimaging, psychiatry and neurosurgery research, and as a target site for Deep Brain Stimulation (DBS) therapy for OCD and major depression (MDD) (Greenberg et al., 2008). Our previous study showed a topographic organization of trajectories from the ventral prefrontal cortex (vPFC), in which a medial-lateral cortical position translates to a ventral-dorsal position in the internal capsule (Lehman et al., 2011), these results were similar in human and monkeys (see poster 605.11).

Hypothesis:
General: The position of a given cortical region determines the location its fibers occupy within the IC.
1. If this hypothesis is correct, we predict that fibers from each of the four functional PFC regions will vary according to their position (dorsal/ventral, medial/lateral, rostral/caudal). Thus, the vPFC fiber position should differ from the dorsal anterior cingulate regions (dACC) and dorsal PFC (dPFC) positions.

2. Within and between each functional region, rules will dictate where fibers are likely to be positioned relative to fibers from other cortical regions, regardless of function.

Each functional area varies on 1, 2, or 3 directions: the dACC in the rostral/caudal dimension; the ventromedial prefrontal cortex (vmPFC) in the rostral/caudal position, and some on the dorsal/ventral dimension; the orbitofrontal cortex OFC in the medial/lateral and rostral/caudal dimensions; the dPFC in all three dimensions.

This study has three objectives:
1. To delineate topographic relationships between pathways from dPFC and dACC compared to the vPFC areas in the IC.

2. To determine organizational rules governing the position of different PFC fiber bundles within the IC.

3. To determine the specific pathways involved at the different DBS sites.

Methods

The PFC was divided into 4 general functional regions: the vmPFC, OFC, dACC and dPFC. Bidirectional tracers (Lucifer yellow, fluororuby, fluorescein) or anterograde tracer (tritiated amino acids) were injected into the PFC in adult Macaca fascicularis PFC (Fig. 1). Fiber bundles were charted and rendered in 3D for each case separately and then combined into one global 3D model. Our experiments were conducted according to the ILAR Guide for the Care and Use of Laboratory Animals (ILAR, National Research Council, 1996) and approved by The University Committee on Animal Resources.
Analysis: 1. Data were first grouped according to the four general functional regions. 2. We then compared injection sites across cases that differ on one specific direction (dorsal-ventral; rostral-caudal, or lateral-medial gradients) but were similar on the other two. 3. To determine the specific pathways involved at the different DBS VC/VS contacts, we used scaled model of the electrode and contact points (Lehman et. al., 2011).

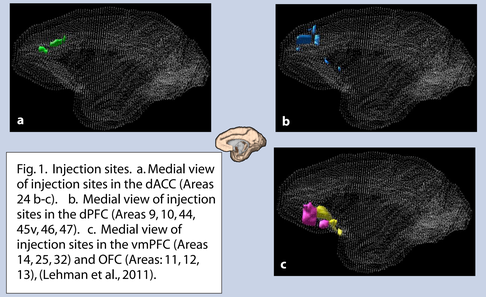


Fig. 1. Injection sites. a. Medial view of injection sites in the dACC (Areas 24 b-c). b. Medial view of injection sites in the dPFC (Areas 9, 10, 44, 45v, 46, 47). c. Medial view of injection sites in the vmPFC (Areas 14, 25, 32) and OFC (Areas: 11, 12, 13), (Lehman et al., 2011).

Results and discussion

1. The position of fibers from different functional regions is organized in dorsal/ventral topography, with those from the vPFC positioned ventral to those from the dACC; dACC fibers are ventral to those from the dPFC. In addition, for vPFC fibers, there is the medial/lateral cortical position that translates to a ventral to dorsal position, (Lehman et al., 2011). Taken together, this places the OFC fibers generally dorsal to those from the vmPFC fibers (Fig. 2).
2. PFC fibers within and between functional regions also show a medial/lateral, dorsal/ventral, and rostral/caudal organization in the IC.
2a. Thus fibers from medial cortical regions travel ventral and slightly medial in the IC to those from more lateral cortical regions (Fig. 3).
2b. Fbers from more dorsal cortical areas travel dorsal to those from more ventral regions (Fig. 4).
2c. Fibers from more rostral cortical areas travel ventral to those originating in more caudal cortical area (Fig. 5 and 6) in the IC.
3. These rules likely interact, creating overlaps between different fiber bundles within the IC. The exact position of the bundle is determined by counterbalance of the three gradients.
4. Each DBS VC/VS electrode contact activates a different subset of cortico-thalamic and brainstem fibers the vPFC as reported previously (Lehman et al., 2011). In addition, the very dorsal contacts capture fibers from the dACC and rostral dPFC. Caudal dPFC fibers are not likely to be not captured directly by any of the DBS electrodes (Fig 7-9).

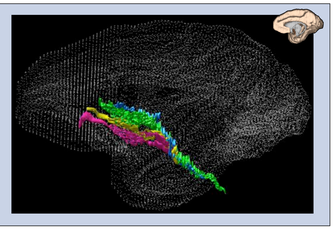


Fig. 2. Topographic organization of prefrontal (PFC) fibers in the Internal Capsule. The 3-D model was derived from computrized model based on tracing studies in monkeys. The position of fibers from different functional regions (vmPFC, OFC, dACC and dPFC) is organized in a ventral to dorsal respectively.

Modulation through the Medial-Lateral Gradient

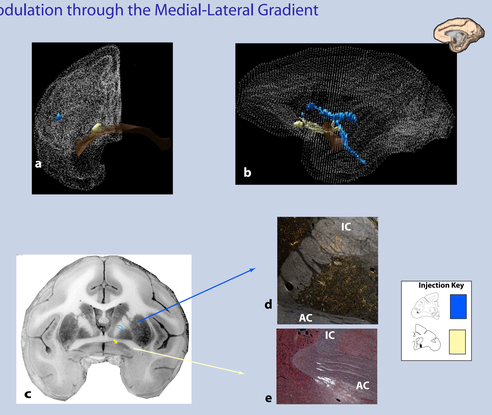


Fig. 3. Pathways of prefrontal cortex differ on the medial-lateral gradient. a. frontal view of the injection sites b. Medial view of the pathways through the IC. c. the topography of fibers in the internal capsule. d. Photomicrograph of the IC for the lateral injection (area 44/47) e. Photomicrograph of the IC for the medial injection (area 13)

Modulation through the Dorsal-Ventral gradient

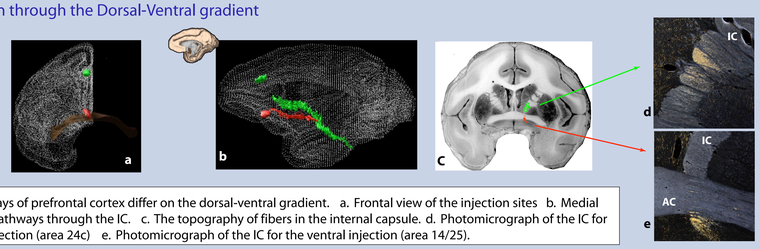


Fig. 4. Pathways of prefrontal cortex differ on the dorsal-ventral gradient. a. Frontal view of the injection sites b. Medial view of the pathways through the IC. c. The topography of fibers in the internal capsule. d. Photomicrograph of the IC for the dorsal injection (area 24c) e. Photomicrograph of the IC for the ventral injection (area 14/25).

Modulation through the Rostral-Caudal gradient

Fig. 5. Pathways of prefrontal cortex differ on the rostral-caudal gradient. a. Medial view of the injection sites and the pathways through the IC. b. the topography of fibers in the internal capsule. c. Photomicrograph of the IC for the caudal injection (area 24b-c) e. Photomicrograph of the IC for the rostral injection (area 24c).

Fig. 6. Pathways of prefrontal cortex differ on the rostral-caudal gradient. a. Medial view of injection sites and the pathways through the IC. b. the topography of fibers in the internal capsule. c. Photomicrograph of the IC for the caudal injection (area 13) d. Photomicrograph of the IC for the rostral injection (area 11/13).

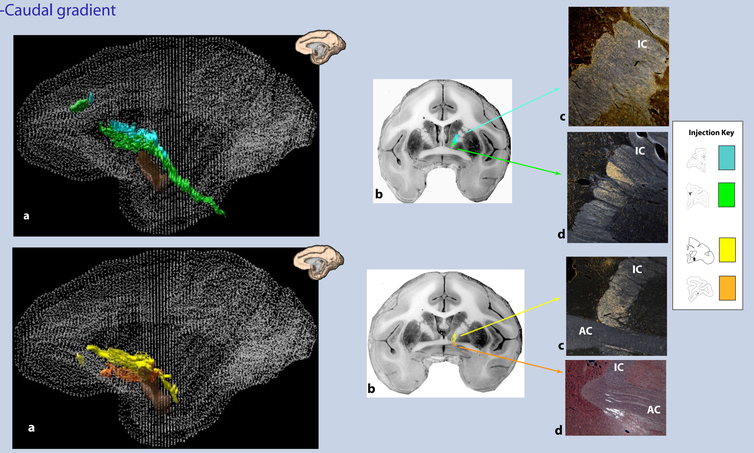
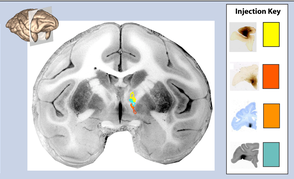


Fig. 7. The topography of pathways from dPFC, OFC and vmPFC traveling through the IC. the diffrent fibers may capture diffrent contacts of the DBS.



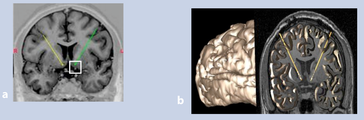
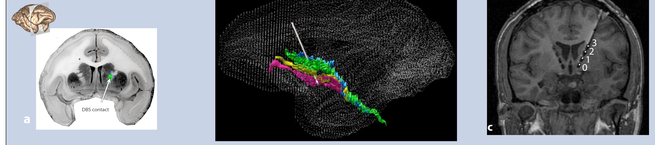


Fig. 8. N. accumbens target for DBS. a. Coronal MRI with electrodes in n. accumbens. b. 3-D reconstruction from human MRI demonstrating

Fig. 9. Pathways through the anterior internal capsule. a. Cross section of brain with electrode contact #3 in IC. b. 3D model, Specific fibers bundles affected will depend on exact location of electrode. ventral contact most likely to capture vmPFC and OFC fibers, dorsal contact most likely to capture dACC and rostral dPFC. c. Ventral anterior internal capsule (VAIC) target for DBS. Coronal MRI with electrodes in the IC and contacts #0 and #1 in the ventral IC.



Conclusions

We found general functional topography of the fiber in the Internal capsule: trajectory from the vmPFC, OFC, dACC and dPFC are organized ventral to dorsal respectively. Our results demonstrate clear rules of organization of the trajectory from PFC according to their positions on the medial-lateral, ventral-dorsal and rostral-caudal gradients. We also found interaction between the three dimensions; hence the relative position of the fibers within the IC determined by counterbalance of the position of cortical injection site along the three gradients. The fact that the exact position of a given efferent fiber bundle will be determined counterbalance by the three gradients, fibers from dorsal and rostral cortical areas, for example, may travel in the IC with fibers originating in more ventral and caudal cortical areas.

Understanding this IC organization is crucial for interpretation of imaging studies. It allows us to predict the possible consequence of lesions and strokes in the IC area. In addition, exploring the PFC-IC directional rules helps understand the effectiveness of DBS and the likelihood that a given PFC functional region may be captured by different DBS contacts(Fig. 9), (see posters, 605.11, 605.14).

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Abbreviations:

ALIC = anterior limb of Internal capsule
dACC = dorsal anterior cingulate cortex
dPFC= dorsal prefrontal cortex
DBS = deep brain stimulation
DTI= diffusion tensor imaging
MDD= major depression disorder
OCD = obsessive compulsive disorder
OFC = orbitofrontal cortex
PFC = prefrontal cortex
VC = ventral capsule
vPFC = ventral prefrontal cortex
vmPFC = ventral medial prefrontal cortex

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