Human and monkey ventral prefrontal fibers use the same organizational principles to reach their targets: tracing versus tractography

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ABSTRACT

A detailed understanding of connectional anatomy is of central importance for both basic and clinical neuroscience. However, in humans, we can only measure anatomical connections using indirect techniques such as MR diffusion tractography, or make indirect inferences from direct measurements in nonhuman primates. Here we present an approach that combines direct tracer measurements in macaque monkeys with diffusion MRI both in macaques and in humans. The approach allows us to provide explicit validation of diffusion tractography and to test the extent to which inferences from macaque can be applied to human neuroanatomy. We focus on the ventral prefrontal cortex (vPFC), whose white matter pathways follow several non-trivial trajectories to reach their targets. Apart from one exception, we found a remarkable overlap between the two techniques in the macaque. Furthermore the organizational principles followed by vPFC tracts in Macaques are preserved in humans.

INTRODUCTION

The gross organization of white matter (WM) bundles has been preserved in evolution between macaques and humans (Thiebaut de Schotten et al., 2012), and similar geometrical features can be observed in both species (Wedeen et al., 2012). This resemblance between species offers us a model for human anatomy when the latter is not practically accessible, and allows us to draw from a large body of knowledge of the macaque functional anatomy. Connectional anatomy of the human frontal lobes is of particular relevance for understanding interpreting human imaging studies.

In this study, we investigate the connectional anatomy of the ventral prefrontal cortex (vPFC) in macaques and humans. Tracing studies in monkeys demonstrate that, while the trajectories of vPFC efferent fibres are complex, three organization rules emerge that allow predictions about where specific fibres are likely to travel (Lehman et al., 2011). First, the uncinate fasciculus (UF) connects not only the vPFC with the temporal lobe, but also serves as a conduit for vPFC fibers to join other white matter bundles. Second, within the internal capsule (IC), fibres from each vPFC area split into a dorsal thalamic and a ventral brainstem group. Third, the medial-to-lateral vPFC position dictates both the route axons take to reach WM bundles and the position they take within the bundle. For example, axons from more medial cortical areas travel ventral to those originating from lateral vPFC regions both in the IC and the corpus callosum (CC). Despite the precision with which such organizational principles can be investigated in macaques, the extent to which these principles apply in the human brains is not clear.

Here we explicitly test this macaque-human prediction by combining accurate mapping of whole WM trajectories from chemical tracing in monkeys, with diffusion MRI tractography in both monkeys and humans. We first compared WM pathways from different vPFC regions using dMRI probabilistic tractography in nonhuman primates to results derived from conventional tracing experiments. We then tested the hypothesis that fibres from

METHODS

We first compared WM pathways from different vPFC regions using dMRI probabilistic tractography in nonhuman primates to results derived from conventional tracing experiments. We then tested the hypothesis that fibres from three different vPFC regions in humans (medial orbital cortex, central orbital cortex, and lateral orbital cortex) use similar rules to reach their targets.

Tracer experiments. Anterograde or bidirectional tracers were injected into each of the three cortical regions. All thick fibers without clear terminal boutons were assumed to be passing fibers and were included in the analysis. Fibers traveling in bundles were outlined as a group and rendered in 3D. Orientation was indicated for each bundle.

For imaging methods, see Figs. 1-2 and attached paper.

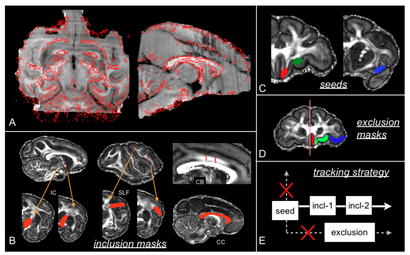

Fig 1. A: Alignment between tracking and tracing macaque brains. Fractional anisotropy map (from tracking data) is displayed as red outlines from high contrast voxels on top of the stacked photographs (from tracing). B: Position of the various inclusion masks used in the macaque tracing experiments of the internal capsule (IC), the superior longitudinal fascicle (SLF), the cingulum bundle (CB) and the corpus callosum (CC). C: Location of the three injection-sites from the tracing data displayed on the FA map. Key: red=vmPFC, green=cOFC, blue=lOFC. D: location of the cortical exclusion masks and the mid-sagittal plane exclusion mask (pink). E: tracking strategy common to both macaque and human experiments. Streamlines are only retained if they cross inclusion masks, and excluded if they don't or if they cross one or more exclusion mask. When two inclusion masks are used, they are required to be crossed in a specified order (anterior to posterior in all our experiments).

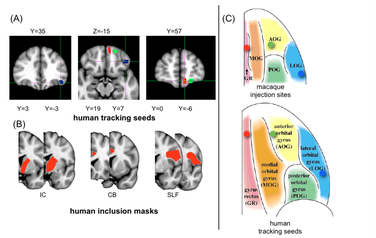

Fig 2. Seed regions (A) and WM inclusion masks (B) used in the human tractography experiments. The slice coordinates are relative to MNI152 standard space, and are in mm (coordinate [0,0,0] corresponds to the anterior commissure). The corpus callosum inclusion mask is not displayed; it corresponds to a single planar ROI containing the whole anterior half of the corpus callosum in coordinate X=0. (C) Position of the seed regions relative to the main orbital sulci in humans and monkeys (figure modified from (Chiavaras et al., 2001)). Key: blue=lOFC, green=cOFC, red=vmPFC.

RESULTS

1. Four vPFC pathways are relatively accurately followed using DTI tractography: the internal capsule (figures 3 and 4), corpus callosum (Fig. 5) , cingulate bundle, (Fig. 6) And uncinate fasciculus (UF (not illustrated).

2. Rules these fibers use in the human brain to reach their targets are consistent with those in the monkey using tracers, including the path fibres take to enter WM bundles, and the position they occupy in the IC and CC (Figs 3, 5, and 6).

3. However, there are specific aspects of these pathways that are difficult to reproduce using tractography in either monkeys or

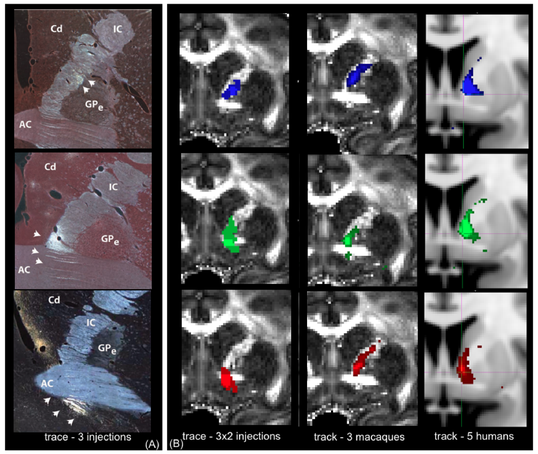

Fig 3. The position of fibres from different vPFC regions travelling in the IC at the level of the anterior commissure (AC). One rule of organization is that axons from medial ventral prefrontal areas travel ventral to those from derived from lateral areas in the IC. Thus the lower row of images are from the mOFC, the central row is from the cOFC, and the top row is from the lOFC. (A) Photomicrographs from single injections placed into each of these regions demonstrating the position fibers take in the internal capsule. (B) 3-D rendering from tracing data in 2 monkeys; (C) tractography data averaged across 3 macaques, middle) and D. Tractography data averaged from 5 human subjects (right). Key: blue=lOFC, green=cOFC, red=vmPFC.

Note the topographic organization is fairly well preserved in the DTI tractography. However, the mOFC fibers travel ventral to the AC or are embedded within it. This is not replicated in neither the monkey nor human DTI tractography. In both cases, the fibers travel above the AC (see Fig. 6).

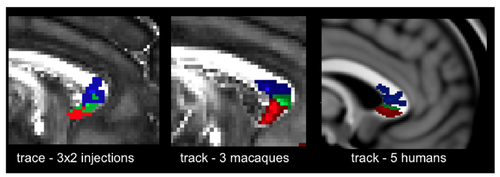

Fig 4. Organization of vPFC projections to the CC. The ventral-dorsal gradient can be clearly seen in both techniques and species. Key: blue=lOFC, green=cOFC, red=vmPFC.

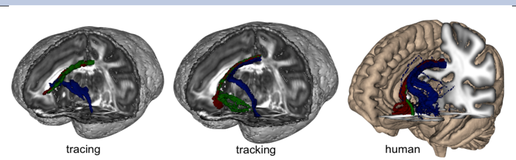

Fig 6. 3D rendering of fibers from lOFC (blue), cOFC (green) and vmPFC (red) areas entering and traveling in the cingulum bundle (CB). The tracing experiments in monkeys show fibers leave the lOFC, travel dorsally, curving around the lateral putamen, to enter the CB. Fibers from the mOFC travel medially in the uncinate fasciculus (not illustrated), then dorsal to enter the CB. Note that the tracking in macaques and humans show essentially the same trajectory.

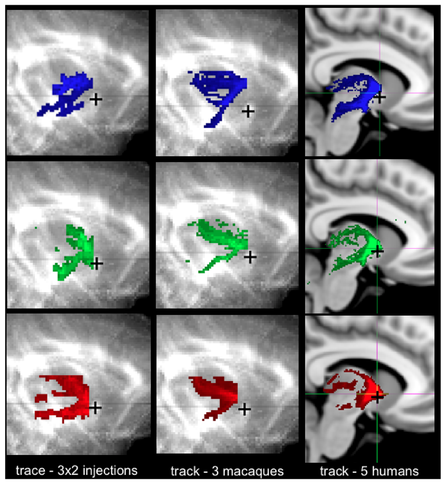

Fig 4. Splitting of the trajectories from the lOFC, cOFC and vmPFC in the IC into dorsal thalamic and ventral brainstem projections. In both species, the splitting occurs immediately caudal to the AC. Key: blue=lOFC; green=cOFC, red=vmPFC. The black crosses show the position of the AC.

CONCLUSIONS

Overall, we found that all organizational principles that were both predicted from chemical tracing in macaques and replicated with macaque tractography, were also present in humans.

1. vPFC fiber bundles rotate from a medial-lateral position in the cortex into a ventral-dorsal gradient in IC and CC.

2. IC pathways separate into dorsal thalamic and ventral brainstem sub-bundles immediately caudal to the anterior commissure.

3. vPFC fibers followed the same route to enter the CB as predicted in the tracing data.

However, the trajectory of vmPFC connections through the IC did not replicate the tracing study. Medial vPFC fibers pass through small fascicles embedded within the ventral striatum . While these small bundles are part of the internal capsule, (Lehman et al., 2011) and are visualized histologically(figure 7B and 7D), they are below the resolution of the DTI image.

These studies set the stage to guide DTI analysis and ROI placements within these bundles and for a better understanding of the changes in white matter tracts associated with disease.

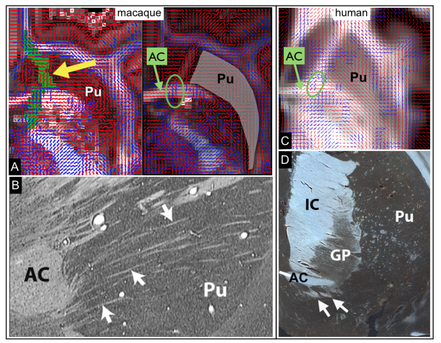

Fig 7. We addressed the problem of why fibers could be traced through and ventral to the AC., A: Fibre orientations from dMRI in the ventral prefrontal cortex, showing, that vOFC pass through a narrow passage within the striatum with noisy fibre orientations (tract shown in green and indicated by a yellow arrow). The principal diffusion direction (bedpostx) is shown in red for each voxel, secondary fibre orientation is shown in blue. Note the crossing fibres through the AC at the exact location of the tracer's route. B: Nissl-stained sagittal section through the macaque brain. Arrows indicate WM fascicles passing through the ventral striatum. C: Fibre orientations from dMRI in humans (one representative subject displayed – axial section). The green circle indicates fibre crossings in the AC. D: GAP-43-stained coronal section through a human striatum. Arrows indicate WM fascicles passing through the ventral striatum. However, while fibers could be potentially traced across the AC an additional problem is that these fibers travel in small fascicles rostrally through the gray matter to reach this level (see B and D). These fascicles are below the MRI resolution. Thus while it may be possible to tract fibers through the AC, the pathways cannot be tract to this point. AC, Anterior commissure; GP, Globus Pallidus; IC, internal capsule; Pu, putamen.

REFERENCES

Behrens TE, et al. (2007) Probabilistic diffusion tractography with multiple fibre orientations: What can we gain? NeuroImage 34:144-55

Jbabdi S, et al. (2012) Model-based analysis of multi-shell diffusion MR data for tractography: How to get over fitting problems. Magnetic Resonance in Medicine [doi: 10.1002/mrm.24204]

Lehman et al. (2011) Rules ventral prefrontal cortical axons use to reach their targets: implications for diffusion tensor imaging tractography and deep brain stimulation for psychiatric illness. J Neuroscience 13;31(28):10392-402.

Abbreviations

AC=anterior commissure
Cd=caudate
dACC=dorsal anterior cingulate cortex
DLPFC=dorsal lateral prefrontal cortex
FEF=frontal eye fields

OFC=orbital frontal cortex
PFC=prefrontal cortex
PMdr=premotor, dorsal rostral
Pu=putamen
vmPFC=ventral medial prefrontal cortex