Non-Invasive Mapping of Corticofugal Fibers from Multiple Motor Areas: useful tool for assessing disconnection after sub-cortical stroke?

J. M. Newton[1,2], N. S. Ward[1], G. J. Parker[3], R. Deichmann[1], D. C. Alexander[4], K. J. Friston[1], R. S. Frackowiak[1]

[1]Wellcome Dept. of Imaging Neuroscience, University College London, London, United Kingdom, [2]Dept. of Neurology, UCLA, Los Angeles, CA, United States, [3]Imaging Science & Biomedical Engineering, University of Manchester, Manchester, United Kingdom, [4]Dept. of Computer Science, University College London, London, United Kingdom

Introduction: Recovery of motor function after subcortical stroke appears to be related to the integrity of descending connections from the ipsilesional cortical motor system. In addition, functional imaging evidence suggests that damage to these descending output fibres may be compensated by increased activity in areas that retain intact corticofugal outputs. Though the trajectories of corticofugal fibres from major components of the motor system through the corona radiata and internal capsule are well-described in non-human primates [1], they have not been described fully in humans. Here we map the trajectories of these connections using probabilistic diffusion tensor tractography in healthy control subjects. We then use this knowledge to assess stroke-induced disconnection of these trajectories and interpret functional re-organization of the cortical motor system, as measured with functional MRI.

Methods: 12 right-handed healthy volunteers and three patients with subcortical stroke (occurring > 20 months previously, resulting in initial weakness of the wrist/hand) were studied. All scans were performed on a 3 T Siemens Allegra MRI System using a standard transmit/receive head coil. Diffusion tensor imaging (DTI), motor event-related fMRI and T_1–weighted structural data sets were acquired for each subject.

DTI acquisition: A cardiac-gated single-shot EPI sequence was used to acquire 64 high diffusion-weighted images (b = 1000 smm^{-2}) and 7 low diffusion-weighted images (b = 100 smm^{-2}) with gradients applied along non-collinear encoding directions. Each image was comprised of 60 axial slices with 2.3 mm^3 isotropic voxels.

Tractography: Data from control subjects were used to map corticofugal connections of the motor system in native space with probabilistic tractography (PICo) that utilized voxelwise crossing fibre information [2,3,4]. The cross-sections of each cerebral peduncle were used as seed points and 1000 streamlines were used to identify the routes of connection from each seed point to anatomically-defined masks of primary motor cortex (M1), dorsolateral premotor cortex (PMd) and supplementary motor area (SMA) in each hemisphere. For each cortical area, binary maps were formed showing voxels that had been hit by at least one streamline from the peduncle en route to the respective area. These maps were transformed into MNI space and summated to produce variability maps of the trajectory to each motor cortical region; the voxel intensities ranged from 1 to 12 and represented the overlap of connections between subjects. These variability maps were then thresholded so that only voxels common to the tracts of 8 or more subjects were retained. These masks were then summated and encoded to show the most common location of tracts connecting the peduncle with M1, PMd and SMA, as well as the overlap of these trajectories.

Patient versus control group comparison of FA: In addition, fractional anisotropy (FA) maps were generated for controls and patients. Following normalization and smoothing, the FA maps of individual patients were compared with those of the group of control subjects on a voxel-wise basis using a one-way ANOVA as implemented in SPM2. Significant reductions in FA were detected at a threshold of $p<0.001$ (uncorrected). These clusters then formed regions-of interest that were overlaid onto the maps showing the most common locations of tracts connecting the peduncle with M1, PMd and SMA.

fMRI data acquisition & analysis: Event-related fMRI data (T_2*-weighted EPI, TE = 30 ms, 48 axial slices, TR = 3.12 s, 248 volumes in total) were acquired while subjects were cued to perform handgrips with either their right or left hand at 20% of their maximum force output for the respective hand. Standard SPM2 preprocessing and statistical analyses were used to generate t-maps of the main effect of hand grip for each hand for each subject. One-way ANOVAs were used to identify significant differences between paretic handgrip activation in individual patients and responses to movement of the same hand for all control subjects at a threshold of $p<0.001$ (uncorrected).

Results & Discussion: Connections were successfully tracked from the cerebral peduncle to M1, PMd and SMA in all control subjects. There was good reproducibility of these trajectories between subjects. Figure 1A shows the most common locations of tracts connecting the peduncle with M1, PMd and SMA, as well as the overlap of these trajectories. The comparative topography of these connections revealed many similarities between humans and other primates [1]. For example, in both the corona radiata and internal capsule the connections between the cerebral peduncle and M1 are located most posteriorly of all the motor system connections studied whereas connections to the SMA were located most anteriorly. For each patient, voxel-wise comparison of FA with the control group revealed focal reductions in anisotropy in the internal capsule and/or corona radiata of the affected hemisphere. In two of the patients studied the areas of reduced FA intersected with the most common locations of motor fiber trajectories. Figure 1B shows this intersection in one of these patients and illustrates likely disconnection of PMd in this individual. We found that these inferred disconnections were associated with enhanced handgrip related responses in the ipsilesional motor system; both patients showed relative overactivation compared with controls in motor areas that were found to have partially disconnected fiber trajectories. Figure 1C shows overactivation of the left precentral gyrus, including PMd, in the same patient whose white matter damage is illustrated in Figure 1B. In contrast, the region of reduced FA in the third patient did not intersect with the trajectories and no enhanced handgrip related responses were found. These results confirm that selective disruption of motor corticofugal fibers influences functional reorganization in individual patients.

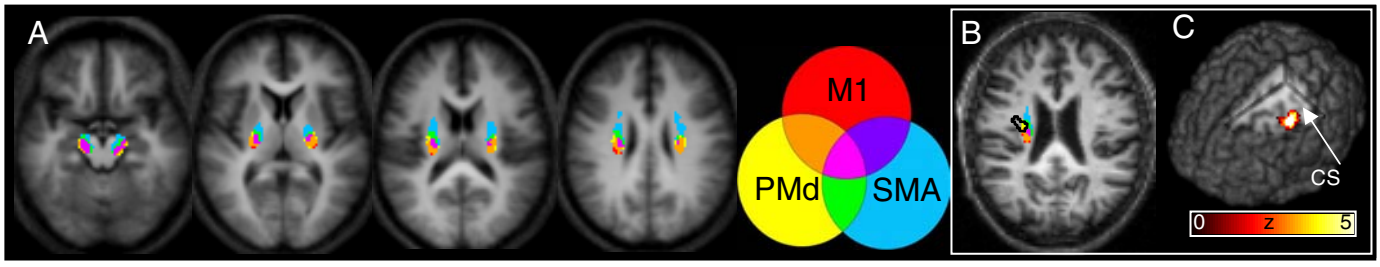

Figure 1: (A) Axial sections showing overlap between the thresholded variability maps (8+ subjects) for M1, PMd and SMA for both hemispheres. **(B)** Sections showing the region of reduced FA in one patient (black outline) over the trajectory overlap map on an axial T_1–weighted section. **(C)** Rendered T_1–weighted image showing significantly greater right (affected) hand grip activation in left precentral gyrus (x = -48, y = -3, z = +51) for same patient compared with the control group. CS = central sulcus

References:

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