Structural Plasticity in Stroke Inferred by Probabilistic Tractography & MEG

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INTRODUCTION: Neural plasticity may play a role in motor recovery after stroke in terms of structural remodeling of white matter in the ipsilesional and contralesional hemispheres and functional reorganization of activity in the sensorimotor cortices. Animal tracing studies show evidence that in the healthy brain, neural activity in the motor areas of both hemispheres are functionally coupled and equally balanced in terms of mutual inhibitory control via transcallosal cortico-cortical inhibitory circuits and stroke may disrupt this balance. Moreover, intra-cortical connections between different regions, such as those between M1 and Ventral Premotor Cortex, show functional asymmetry. Previous in vivo human studies have not mapped completely these important networks and therefore we have attempted to map and investigate the structural connectivity of the network involved in hand motor function, by combining time-frequency reconstructions of magneto-encephalography (tfMEG) data, with HARDI diffusion MR data, in 4 controls and 4 stroke subjects assessed before and after a novel rehabilitation intervention (3).

METHODS: We studied 4 stroke subjects in subacute/chronic phase after a stroke in the sensorimotor cortex of the right hemisphere and 4 normal subjects. The stroke subjects received sensorimotor neurorehabilitation training of the upper extremity, delivered by a robotic device, for 45 minutes, 3 times/wk over 6 weeks (18 sessions). The patient function was assessed with Fugl-Meyer(/66), Grip strength (Kg), and WMFT (s). **Imaging Protocol and Data Processing:** High-angular resolution diffusion imaging (HARDI) datasets (55 directions, b=2000 s/mm2, 2.2 mm per side isotropic voxels) acquired before and after a robotic neurorehabilitation intervention for the stroke subjects. The same imaging protocol was applied to the four normal subjects in a single session. MEG imaging was performed with self-paced tapping of the index finger tapping every 3 seconds (3). For fiber tracking we used probabilistic q-ball fiber tracking algorithm (1). The probabilistic algorithm was developed in our laboratory and is based on previously validated non-parametric estimates of the uncertainties in fiber tracking directions (2). Additionally bootstrap methods have been developed to estimate the probability of connectivity which provides the probability of detecting connections between two areas for a given algorithm. The hand motor network connected to M1 was tracked by seeding M1 based on the hand motor task based tfMEG activations in the stroke and control subjects. The MEG generated from movement of the contralateral finger were used to define the M1 regions. Target regions were defined based on neuroanatomical landmarks as suggested from previous motor network studies.

RESULTS: Seeding in MEG-based Hand Motor Region with q-ball probabilistic fiber tracking in 4 control subjects, we successfully mapped the structural connectivity of the motor network yielding the known motor pathways: Ipsilateral Corticospinal Tract (CST); Inter-Hemispheric connections between the two M1 regions and between M1 and contralateral Dorsal Premotor Cortex (PMC); Inter-Regional connections between M1 and Non-Primary Motor areas: Posterior Parietal Cortex; Primary Sensory Cortex (S1); Ventral and Dorsal Premotor Cortex, Supplementary Motor Area (SMA) and Basal Ganglia (BG) (Fig.1). When seeding in MEG-based Hand Motor Region of the ipsilesional and contralesional hemispheres in stroke patients with different degrees of recovery after neurorehabilitation we observed improved structural connectivity for the ipsilesional M1 connections to contralateral M1 and to the ipsilesional ventral PMC in the patient with the best recovery score after the neurorehabilitation intervention and different degrees of structural changes that correlate with the functional outcome in the other 3 patients. While our connectivity metric was already at 100% for the CST we observed an almost doubling of the visitation number (Fig.2). The spatial probability maps of the best improved stroke patient show reliable connections from M1 to CST and from M1 to PMv in which >50% of bootstrap connections were found in voxels between the seed and target regions (red). However, for M1 to M1c there are less reliable connections with <<50% of bootstrap connections (light blue) (Fig. 3)

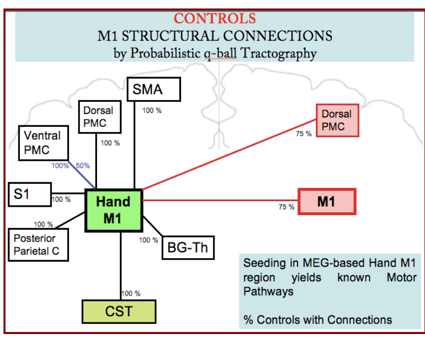

Fig.1

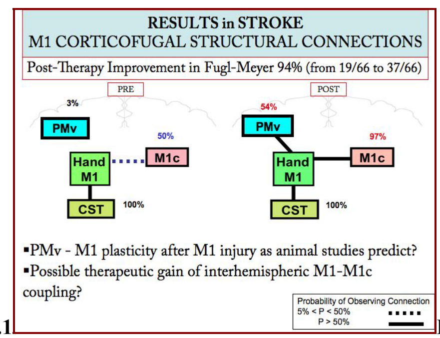

Fig.2

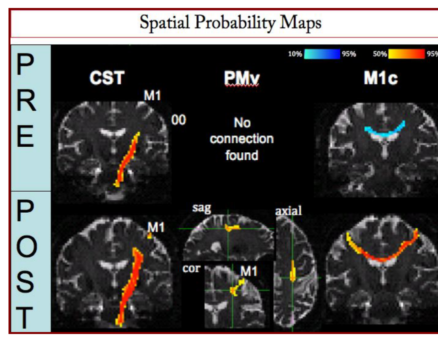

Fig.3

DISCUSSION: Our preliminary results are consistent with existing evidence from animal tracing studies showing plasticity over time of the structural connectivity of the regions involved in the hand motor network. In particular increased M1 connections to the ipsilesional ventral PMC were found in animal studies in response to M1 injury and also found in this case using MEG and a probabilistic tractography. Secondly, we observed improved connectivity to the contralesional M1, which may reflect return toward normative inhibition of the contralesional M1; this interpretation is further supported by the post-therapeutic increased MEG activation in the ipsilesional M1 compared to the contralesional M1. We have successfully demonstrated the ability of probabilistic q-ball fiber tracking to delineate the hand motor network. This network has not been previously well characterized and the variability of these connections in humans remain unknown. Our preliminary data has also successfully delineated the previously unmapped connection between M1 and intra-hemispheric ventral PMC in humans. This connection was previously found to be functionally lateralized. We have found lateralization in 2 of 4 controls and in one control the apparent absence of inter-hemispheric connections. Further studies are needed to map out and quantitatively characterize the normal hand motor network in humans. Structural information derived from probabilistic q-ball fiber tracking combined with the functional data from tfMEG, enables better interpretation of the underlying plastic changes in stroke and significant improvement over current methods to delineate and map the connections of the motor network in stroke. The structural changes seen in the post- versus pre-therapy comparisons between the Intra-hemispheric and Inter-hemispheric cortico-cortical connections may become a strong independent predictor of motor recovery.

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