In vivo measurement of conduction velocity and axon diameter properties in the human brain

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Introduction:

Previous ex-vivo studies, performed on exited nerves, had shown that the Axonal Conduction Velocity (ACV) of myelinated fibers is proportional to its diameter (1). Recent studies have succeeded to measure the rat brain (2) and the human brain (3) axon diameter distribution (ADD) in-vivo, using AxCaliber - a diffusion MRI based methodology (4). In this study we investigated the correlation between human visual callosal fibers' ADD to its ACV which was measured through EEG recording and behavioral tasks across a cohort of 20 subjects.

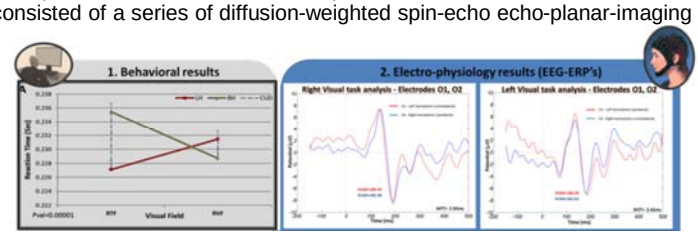
Methods:

Subjects: 20 right handed subjects (10 male and 10 female) underwent behavioral paradigm, EEG and MRI (AxCaliber).

Behavioral paradigm: The subjects underwent a manual RT task according to Poffenberger paradigm (5) to measure the Inter Hemispheric Transfer Time (IHTT). Subjects were required to press a button in response to lateralized presented stimuli while maintaining fixation in the center of the screen. Four fields were determined: two visual fields (left visual field (LVF) and right visual field (RVF)) and two hand sides (left hand (LH) vs. right (RH)). Then, the RT-based IHTT (crossed-uncrossed difference (CUD)) was calculated by subtracting the average RT of the two uncrossed response conditions (LVF-LH, RVF-RH) from the average RT of the two crossed conditions (LVF-RH, RVF-LH).

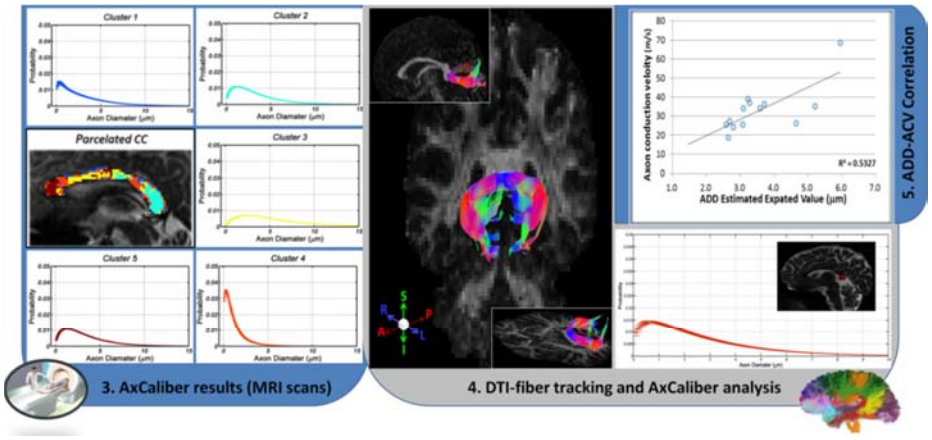
EEG Protocol: The subjects underwent EEG recording using a 64-channel, BioSemi ActiveTwo system. In the EEG experiment, subjects were required to count the fixation point color changes while lateralized stimuli were presented. The component N160 (O1/O2, PO3/PO4 and PO7/PO8 electrodes) is known for indicating the brain visual stimuli reception. The differences for each Component between the two hemispheres measure the IHTT.

MRI protocol: Subjects underwent MRI scan (GE 3T). Experimental protocol consisted of a series of diffusion-weighted spin-echo echo-planar-imaging acquisitions. The experiment was repeated for 4 different diffusion times (Δ): 87.7, 67.4, 47.7 and 27.7ms with the following parameters of TE=137.5, 123.7, 112.7 and 106.7ms respectively. All other parameters were fixed: δ=21ms, TR=6,000ms, FOV=192mm^2 and resolution of 1.5mm^3 at sagittal plane. 28 diffusion gradient increments (linearly from 0 to 4G/cm) were applied along x-direction, which is perpendicular to the corpus callosum (CC). Voxel-by-voxel analysis was performed on the mid-sagittal slice using AxCaliber framework (4). The output parameters of AxCaliber (gamma function parameters and volume fraction of the diffusion components) were used as an input to a clustering analysis (k-means) with 5 clusters.



Results:

1. Behavioral results match the previous findings with the Poffenberger paradigm. The IHTT for stimuli presented to the ipsilateral side were shorter than the contralateral side in the visual trails. We were also able to reconstruct the asymmetric IHTT phenomenon and find that the CUD from the right to the left hemisphere is faster than the CUD from the left to the right hemisphere. **2**. Physiological results (EEG-ERP's) were varied among subjects. In most cases, The IHTT for stimuli presented to the ipsilateral side was shorter than the contralateral side. The N160 component indicates the visual input from the left visual filed and Right visual field between the right hemisphere (blue) and the left hemisphere (Red) .**3**. Using AxCaliber we were able to segment the CC and find variation between subjects' ADD along the CC. **4**. Definition of the visual callosal fibers was done by segmenting each subject individually to its native space Brodmann's map, followed by fiber tracking Analysis (using ExploreDTI(6)) on the primary visual regions (BA17). Using the CC mid sagittal slice and the extracted visual fibers, the exact crossing location in the CC was set for AxCaliber analysis. Additionally, each subject's visual fibers length were measured and then divided by its IHTT for ACV calculation. **5**. The analysis process for all three experimental procedures was successful on 13 out of the 20 subject. 2 subjects were omitted due to brain structure abnormalities, 3 were omitted due to extremely low EEG SNR and 2 more due to AxCaliber analysis failure. The correlation between ADD and ACV (N=13) was found to be significant (r=0.73/p=0.0046) indicating a relation between conduction velocity and the axon diameter.



Conclusions:

AxCaliber is an indirect technique that measures the axon diameter distribution and thus must be validated. Although histological measures do find correlation between the measured ADD and computed ADD, corroborate the ADD measure by physiological measures is essential. In this work we were able, for the first time, to correlate the axon diameter and conduction velocity in the living human brain. This work indicates that AxCaliber is a reliable parameter of the axon diameter and can be used to infer on white matter physiology.

This work presents a linear correlation between white matter micro-structure and its electrophysiology in a living human brain.

References:
1. Gasser et al,1939; 2.Barazany et al,2009; 3.Horowitz et al. 2012; 4.Assaf et al, 2008; 5. Poffenberger,A. T.1912; 6. A. Leemans et al, 2009.