IN VIVO DIFFUSION SPECTRUM IMAGING SHOWS THE STRUCTURAL BASIS OF THE "PAPEZ CIRCUIT"

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Background: The "Papez circuit" is an important neuronal circuit representing one of the anatomical substrate of memory and emotion (1, 2). It originates from the hippocampus (cornus ammonis and dentate gyrus) and the subiculum, goes through the fornix and finally projects to the mamillary body and the septal region, figure 1 (bottom left). The mamillary bodies are also connected to the anterior thalamic nuclei through the mamillo-thalamic tract and the subiculum projects to the cingulated cortex. Previous studies showed atrophy in structures constituting the "Papez circuit" in patients with temporal lobe epilepsy (3) and Alzheimer disease (4). To date, however, no attempt has been done to show the structural basis of the connecting structures *in-vivo*, probably due to its convoluted shape and complex nature. In this investigation, we aimed at disentangling the anatomical structure of the "Papez Circuit" in humans using high-angular resolution diffusion spectrum imaging (DSI).

Methods: Six healthy female subjects (Age: 26±4) underwent magnetic resonance DSI at 2 different 3 T scanner (Magnetom Trio a Tim System, Siemens, Erlangen, Germany) using a 32 channel head coil. (TR/TE=6600/138, FoV=212 mm, 34 slices, 2.2 mm isotropic resolution, 258 diffusion directions, b=8000 s/mm^2, 2 repetitions). Protocols at scanner 2 (two subjects) were slightly adapted in slice thickness and echo time (slice thickness=2.4 mm and TE=136ms). High-resolution MPRAGE images were acquired for anatomical reference (TR: 2400 ms, TE: 3.59 ms, 0.8 mm isotropic resolution, FOV256x256). DSI tractography was performed based on a streamline algorithm using the TrackVis software (curvature ≤ 45°) (5). On the basis of MPRAGE images and a stereotaxic atlas of the human brain (6), 3D ROIs were selected to identify: 1) the dentate gyrus and subiculum of the hippocampus; 2) the crus fornicis 3) the body/anterior pillar of the fornix 4) the mamillary body and 5) the thalamus.

Results: Using DSI in humans we were able to visualize *in vivo* the structure of the "Papez circuit". In all six subjects, we could consistently map the Hippocampus-mamillary body pathway among: 1) the subiculum of the hippocampus (Red ROI) 2) the crus fornicis (yellow ROI) 3) the body/anterior pillar of the fornix (orange ROI) and 4) the mamillary body (light blue ROI), figure 1 and 2A. We could also track the pathway connecting the lateral subiculum (violet ROI) to the cingulated cortex (light blue and green ROI), figure 1 and 2B; this tract is considered to complement the hippocampus-mamillary body function in cognition and memory. In addition, we could map the tract connecting the mamillary body (light blue ROI) to the thalamus (violet ROI), figure 1 and 2C, where higher level integration of the mnesic and emotional information is performed. One subject was scanned in both scanners 1 year apart. In both scans, the Papez circuit was consistently detected.

Conclusion: In this work, we reveal for the first time *in vivo* the structural basis of the "Papez circuit", which is one of the most important anatomical substrate for emotion and memory in humans. Results were consistent in 6 healthy subjects and across used scanners.

State-of-the-art diffusion imaging techniques such as DSI appear to be a very promising non-invasive imaging method to characterize complex anatomical structures *in-vivo* and to subsequently investigate diseases–related anatomical disruptions and responses to therapy.

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