The medial forebrain bundle - A forgotten structure in the human brain identified with statistical fiber mapping

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Introduction: The medial forebrain bundle (MFB) is classically regarded as a structure of the reward circuitry and is a key structure of the mesolimbic-dopamine system, a system related to affective disorders, drug addiction, and learning [1]. The MFB is a bundle of loosely attached fibers that connect the ventral tegmental area VTA, the lateral hypothalamus, ventral striatum, accumbens nucleus AcN, and septal area. It is a bi-directional structure and contents shorter and longer ascending as well as descending tributaries, which enter and leave the MFB as small fascicles [2]. The MFB constitutes a core structure of a distributed network that serves as a neural surrogate of wanting and liking [3]. The natural function of this circuitry is to predict and compute rewards in the environment, initiate thorough exploration, foraging and exhibits an investigatory repertoire (the wanting) with culmination in individual and environmentally dependent consummatory behaviour (the liking). The MFB is a well studied and characterized structure in the rodent and is mainly located in the lateral wall of the hypothalamus. There are two major parts to this bundle. The medial part follows the lateral wall of the third ventricle and connects the lateral hypothalamus to the reticular formation of the brainstem (descending fibers). The lateral part of the MFB is directed lateral and caudal at the level of the substantia nigra SN. The dopaminergic neurons that project with the MFB originate mainly in the VTA. The MFB as a structure of reward and motivation has been extensively studied in rodents, however, to our knowledge there is no consensus as to where it is located in the human. Classical atlases of the human CNS present an idealized depiction of the MFB, showing it as a connection highway between the upper brainstem and the anterior portion of the hypothalamus. Even in the more detailed atlas by Mai et al. [4] it is only shown as a fiber tract that starts anterior to the subthalamic nucleus STN but the full structure evidently lacks continuity. We introduce an approach by which we were able to robustly identify the MFB as a well separated structure to the ATR and its implication for deep brain stimulation DBS in movement disorders and depression [5,6].

Methods: The MR-imaging protocol comprised standard high resolution imaging protocols commonly used in Neuroradiology. Data were acquired on a 3.0T whole body MR imaging system using an eight-element phased-array head coil. For the purpose of brain mapping and registration to MNI space an magnetization prepared rapid acquisition gradient echo (MPRAGE) with isotropic 1mm resolution was used. The 3D-MPRAGE sequence was acquired before (structural information) and after (vessel visualization) contrast administration (Gadolinium DTPA) with a SENSE factor of 4, TR=8.5 ms, TE=3.8 ms, flip angle 8°, FOV 256mm, matrix 256 x 256, 160 slices, slice thickness 2 mm, acquisition time 4:17 min. Furthermore an isotropic T2-weighted Fast Spin Echo FSE (TR=12650 ms, TE=100 ms, FOV 254 mm, matrix 176 x 176, 120 slices, slices thickness 1.44 mm, acquisition time 3:44 min.) was used for the visualization of midbrain nuclei and identification of seedpoint ROI's for fiber tracking. Diffusion tensor imaging (DTI) facilitated a sensitivity encoded (SENSE, factor 2.9) spin-echo echo-planar imaging (SE-EPI) pulse sequence with TR=13188 ms, TE=84 ms, FOV 256mm, matrix 128 x 128; 70 slices, slice thickness 2 mm, number of gradient directions: 32, b-value=1000 s/mm², acquisition time 7:54 min.) All images were conducted in axial orientation.
Data from 26 subjects were analyzed. Deterministic fibertracking (dFT) of the anterior thalamic radiation (ATR) and medial forebrain bundle (MFB) was performed with StealthViz (Medtronic Navigation, Louisville, USA), probabilistic FT with FSL-probtrac (FMRIB, Oxford, GB). Subsequent image registration, statistical mapping and elastic registration onto the MNI152 brain template were done with FSL. The elastic registration of all individually fiber tracts from all subjects resulted into statistical fiber probability maps in the MNI152 standard space. 3D-Rendering and Visualization was performed in Amira 5.4 (Visage Imaging GmbH, Berlin, Germany).

Results: In humans the MFB is a far more complex structure than in rodents owing to the phylogenetic development of the human brain. It seems to be a truly bipartite structure with the main trunk splitting into two parts that follow distinct directions. Proximal to the VTA the main trunk connects to the deep nuclei of the cerebellum. Form here it ascents, following the superior cerebellar peduncle and the upper pons, retrorubral area and periaqueductal grey PAG. At the VTA the structure partitions into an infero-medial branch (imMFB) and a supero-lateral branch (slMFB). The imMFB represents the traditional description of the MFB in rodents. The statistical fiber maps reveal that the slMFB parallels the ATR, intermingles to a certain extend in the internal capsule and also shows a direct access to the ventral striatum and AcN [5,6].

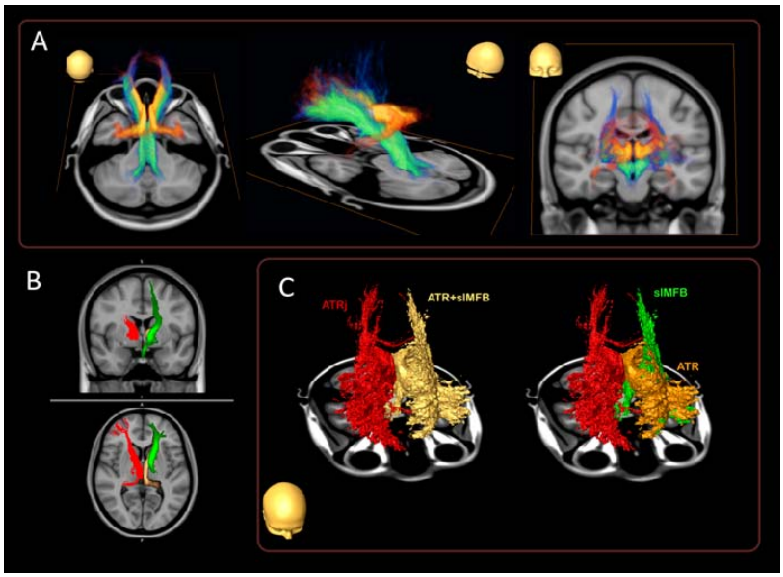

Fig.1: 3D-visualization of the MFB (green) and ATR (gold).

A) statistical fiber probability maps derived from individual deterministic FT from 26 subjects, subsequently warping to MNI-space and spatial averaging. Colour density reflects probabilities between 20-100%.

B) comparison of the ATR from JHWM-atlas [9] (red-left side) and our separation into ATR (gold) and MFB (green) (right side).

C) 3D-full render of the Johns Hopkins WM-atlas ATR (red) and our derived ATR+MFB (yellow) on the left side. The combined structure of ATR+MFB was derived by masking at 20% of our probabilistic fiber maps. The identity of both structures can be appreciated.
Nevertheless the separation as derived from our tracking evidently depicts two separate pathways - the superior-lateral branch of the MFB (green) and the ATR (cupper).

Discussion: The neuroanatomy of the MFB shows remarkable differences between rodents and humans. In rodents the MFB is large but a compact heterogeneous pathway that is a massive connection highway for integrating lower and higher brain functions whereas in humans the MFB depicts as a truly bipartite structure. It is evident that the MFB contains the major brain system that is responsible for a variety of drug addictions [7]. Thus, one could imagine that inadvertently caused stimulation of the MFB during STN DBS-stimulation could be addictive [6] but also the possibility of localized DBS of the slMFB may skirt some of the other brain processes that produce addiction [6,8].

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