Characterization of the Human Habenula in-vivo and ex-vivo at 7T

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Introduction: The habenula has an important controlling role within the human reward system [1,2]: positive reward is signaled by the dopamine system, whereas disappointment is linked to habenular activation. Overactivation of the lateral habenula is associated with depression [3,4]. The habenula is positioned next to the third ventricle in front of the pineal body. It is divided into a medial and lateral part, which receive input from frontal parts of the brain via the stria medullaris and project down the brainstem via the fasciculus retroflexus[5]. The habenular commissure connecting the nuclei on both hemispheres forms the habenular trigone. However, the visualization of this structure is difficult because of its rather small size of approximately 5-9 mm in diameter. Therefore, we made use of a high field strength of 7T to obtain high resolution and high contrast T1, T2* und proton density maps to visualize and determine structural subdivisions of the habenula in-vivo and ex-vivo.

Methods: All experiments were performed on a 7 Tesla whole-body MR scanner (MAGNETOM 7T, Siemens Healthcare, Erlangen, Germany) using a 24 channel phased-array head coil (Nova Medical Inc, Wilmington MA, USA) for in-vivo scans, and a custom-built single channel square coil (120mm side) with the post mortem brain tissue centred inside. The study was approved by the ethics committee of the local university and informed consent was obtained. Post mortem brain was fixed in 4% formalin 24 hours after death (female, 65 years old, cardiac failure).

In-vivo: High-Resolution whole-brain T1 maps were acquired using an MP2RAGE [6] sequence with the following parameters (TR=4520ms, TE=3.8ms, TI1=100ms, TI2=3500ms, bw=170Hz/px, 0.8 mm isotropic, flip angle $_{1,2}$=4°). Maps of T2* were acquired using a spoiled gradient-echo sequence with a range of echo times (TR=49ms, TE1=8.2ms, TE2=15.3ms , TE3=22.43ms, TE4=29.57ms, bw=200Hz/px, 0.8 mm isotropic, flip angle=15°). The maps were co-registered, and the habenula was identified by visual inspection and comparison with surrounding macroanatomical landmarks [7, 8].

Ex-vivo: T1 maps were acquired using MP2RAGE [6] (TR=3000ms, TE=7.38ms, bw=170Hz/px, 0.15 mm isotropic, flip angle=8°) and maps of T2* using a spoiled 3D gradient-echo sequence (TR=35, TE1=7.7, TE2=15.4, TE3=23.0, 0.25mm isotropic, flip angle=10°). Additionally, to minimize the effects of T1 and T2, we used a 3D gradient-echo sequence with a range of echo times (TR=1000ms, TE1=6.3, TE2=16.68, TE3=27.06, TE4=37.44, TE5=47.82, TE6=58.20, TE7=68.58, TE8=78.96, 0.25 mm isotropic, flip angle=68.4°) and calculated a map of the density of protons in the imaged volume ($S=S_0 \times \exp[-TE/T2^*]$) [9, 10].

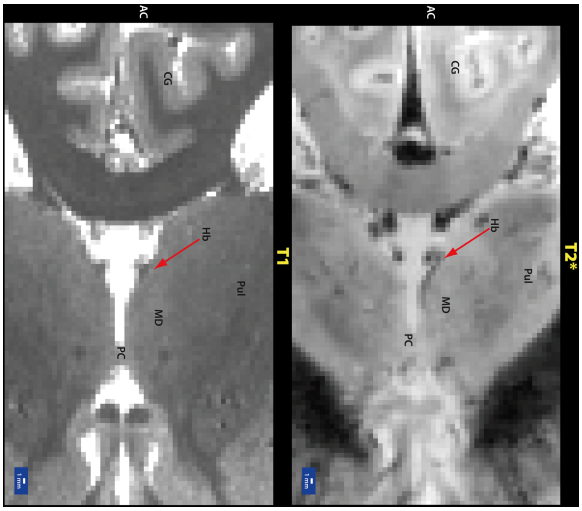

Fig 1: Habenula *in vivo* (horizontal view, T1=2173.3 ms, T2*=27.5 ms) Hb: habenula, PC:posterior commissure, AC: anterior commissure, CG: corpus callosum, MD: medialdorsal thalamus, Pul: pulvinar

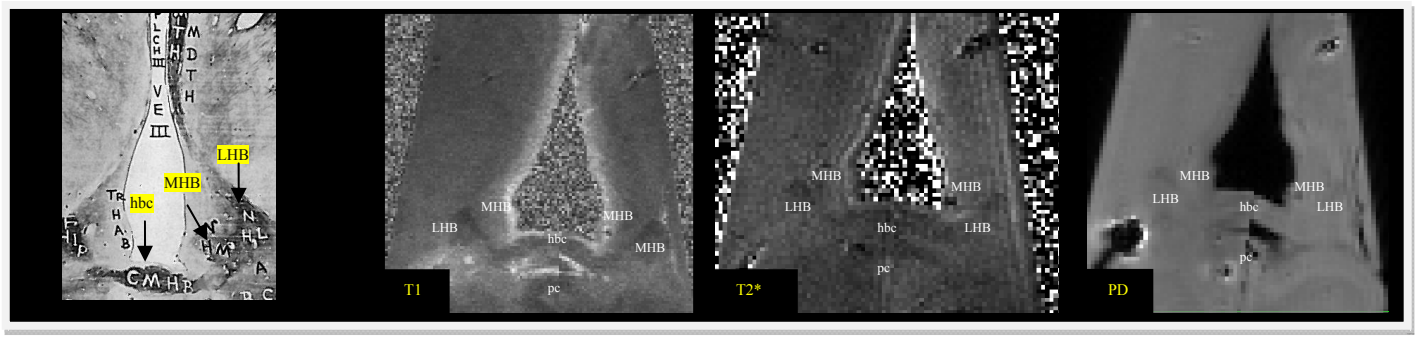

Fig 2: Habenula *ex vivo* (horizontal view): Map of T1, map of T2*, and proton density map show distinct lateral and medial habenular nuclei according to myelin stain sections (adapted from [11]) MHB: medial habenula, LHB: lateral Habenula, hbc: habenular commissure, pc=posterior commissure, Aq=aqueduct

Results and Discussion: The habenula can be easily identified in-vivo in calculated parameter maps of the relaxation times T1, and also T2*, as a small nucleus medial to the caudal part of the dorsal thalamus, directly below the ventricular surface (Figure 1). T1 images show strong contrast of the habenula with surrounding brain tissue that typically results from high myelin content. Probably due to a concomitant high iron content, the habenula also shows reduced T2* compared with neighboring regions. On high resolution ex-vivo maps of T1, T2* and proton density, the medial and lateral nuclei of the habenula (Figure 2) can be discriminated on single axial slices. The medial habenula (MHB) shows less contrast with surrounding brain tissue than the lateral habenula (LHB), or the habenular commissure, which show up quite plainly in maps of T1, T2* and proton density.

Conclusion: MRI at 7 T shows the human habenula in-vivo equally clearly in T1 and T2* maps. Thus it is likely to be characterized by a high concentration of both myelin (T1 decrease) and iron (T2* decrease). We found structural subdivisions of the habenula in ex-vivo MRI: lateral and medial habenula, with their commissure, which form the habenular trigone. Studies of habenula contrast, as it reflects iron and myelin content, and of its subdivisions, are the subject of further research, which may also assist investigation of the pathophysiology of a wide range of neurologic and psychiatric disorders.

References: [1] Matsumoto, et al. Nature 2007, 447, 1111-1115.[2] Ullsperger, et al. J. Neuroscience 2003, 23, 4308-4314.[3] Sartorius, et al., Med. Hypotheses 2007, 69, 1305-1308. [4] Sartorius, et al., Biol. Psychiat. 2010, 67, e9-e11.[5] Hikosaka, et a. J. Neurosci. 2008. 28, 11825-11829.[6] Marques, Neuroimage 2010. 49, 1271-1281.[7] Mai et al., 2008. [8] Nieuwenhuys, et al., 2008. [9] Neeb et al., Neuroimage 2006. 1;31(3):1156-68. [10] Warntjes, et al. MRM 2007. 57(3):528-37. [11] Riley, 1943, 427.