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In-vivo quantitative structural imaging of the human midbrain and the superior colliculus at 9.4T

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ABSTRACT

We explored anatomical details of the superior colliculus (SC) by in vivo magnetic resonance imaging (MRI) at 9.4T. The high signal-to-noise ratio allowed the acquisition of high resolution, multi-modal images with voxel sizes ranging between $176 \times 132 \times 600$ μm and $(800)^3$μm. Quantitative mapping of the longitudinal relaxation rate R1, the effective transverse relaxation rate R2*, and the magnetic susceptibility QSM was performed in 14 healthy volunteers. The images were analyzed in native space as well as after normalization to a common brain space (MNI). The coefficient-of-variation (CoV) across subjects was evaluated in prominent regions of the midbrain, reaching the best reproducibility (CoV of 5%) in the R2* maps of the SC in MNI space, while the CoV in the QSM maps remained high regardless of brain-space. To investigate whether more complex neurobiological architectural features could be detected, depth profiles through the SC layers towards the red nucleus (RN) were evaluated at different levels of the SC along the rostro-caudal axis. This analysis revealed alterations of the quantitative MRI parameters concordant with previous post mortem histology studies of the cyto- and myeloarchitecture of the SC. In general, the R1 maps were hyperintense in areas characterized by the presence of abundant myelinated fibers, and likely enabled detection of the deep white layer VII of the SC adjacent to the periaqueductal gray. While R1 maps failed to reveal finer details, possibly due to the relatively coarse spatial sampling used for this modality, these could be recovered in R2* maps and in QSM. In the central part of the SC along its rostro-caudal axis, increased R2* values and decreased susceptibility values were observed 2 mm below the SC surface, likely reflecting the myelinated fibers in the superficial optic layer (layer III). Towards the deeper layers, a second increase in R2* was paralleled by a paramagnetic shift in QSM suggesting the presence of an iron-rich layer about 3 mm below the surface of the SC, attributed to the intermediate gray layer (IV) composed of multipolar neurons. These results dovetail observations in histological specimens and animal studies and demonstrate that high-resolution multi-modal MRI at 9.4T can reveal several microstructural features of the SC in vivo.

Introduction

In-vivo magnetic resonance imaging (MRI) studies of the midbrain are challenging due to the small size and proximity of its nuclei and structures, and often unknown sensitivity to MR contrast mechanisms. MR imaging of midbrain structures has considerably improved in recent years due to advances in technology, including an increased availability of high field scanners, tailored sequence development, and optimized post-processing methods for brainstem imaging (for a recent review see Sclocco et al., 2018).

Both signal-to-noise ratio and image contrast increase with field strength which consequently enables the acquisition of high resolution

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images within reasonable acquisition times (Pohmann et al., 2011, 2016). The effects of local differences in magnetic susceptibility are particularly prominent at high magnetic field strengths (Budde et al., 2014; Duyn et al., 2007) and therefore enable a better definition of deep brain nuclei (Deistung et al., 2013a, 2013b; Sclocco et al., 2018; Stüber et al., 2014). Multiple studies reported the delineation of the red nucleus (RN) and substantia nigra (SN) at 7T using magnitude images of T2* weighted sequences (Abduljalil et al., 2003; Bourekas et al., 1999; Eapen et al., 2011). Due to the increase of the susceptibility-effect at high field, phase images also provided enhanced contrast in cortical and deep brain structures revealing details that were not visible in magnitude images (Abduljalil et al., 2003). However, phase and magnitude images represent non-local contrast mechanisms that show orientation-dependence and cannot be easily compared across subjects, thus impeding reproducibility (Li et al., 2011). The use of quantitative relaxometry measures, such as mapping of the longitudinal (R1), the transversal relaxation rates (R2 or R2*), and quantitative susceptibility mapping (QSM) are emerging for the in vivo study of deep brain anatomy potentially yielding more reproducible results. These parameters are influenced by the presence of myelin and iron in the brain and the combination of different maps may reveal local features based on the cyto- and myeloarchitecture of tissues (Deistung et al., 2013b; Deoni, 2010; Stüber et al., 2014).

Deistung et al. (2013a) reported the delineation of the boundary between the SN and the subthalamic nucleus (STN) using QSM at 7T for the first time. Deistung et al. (2013a) also reported multiple fiber tracts in the midbrain as well as SN and RN subdivisions, which were not visible in other quantitative maps. Forstmann et al. (2014), delineated the STN and SN and created probabilistic maps based on these findings. Several studies used a combination of diffusion based, T2 and T2* weighted MRI to automatically delineate several midbrain nuclei and provided probabilistic information on their location and extent (Abduljalil et al., 2003; Bianciardi et al., 2015, 2018; Forstmann et al., 2014; Keuken et al., 2014; Lorio et al., 2016). Several of these in vivo findings are available as MNI-based atlases, thus bridging the gap between in vivo data and previous atlases based on histology (Ewert et al., 2017). Beyond the critical importance of MNI space coregistration for the transfer of anatomical information across studies, it may support the detection of subtle anatomical detail with low contrast to noise ratios, in case these show spatial congruency across individuals and across normalized images from multiple individuals.

While the more prominent midbrain nuclei, particularly the STN and SN, have already received much attention in high field MRI imaging, the superior colliculus (SC) has not been investigated in detail, despite its potential role in several neurological diseases. Alterations of the SC's structural integrity, functional properties, and connections are reported to occur in patients with degenerative diseases and in animal models of degenerative diseases, such as dementia with Lewy bodies (Erskine et al., 2017), Alzheimer's disease and progressive supranuclear palsy (Dugger et al., 2011; Terao et al., 2013), amyotrophic lateral sclerosis (van Zundert et al., 2008), and cervical dystonia (Holmes et al., 2012; Hutchinson et al., 2014). Visual and oculomotor impairments in patients with Parkinson's disease are associated with pathological changes of brainstem networks including the SC (Cubizolle et al., 2014; Diederich et al., 2014; Rolland et al., 2013; Terao et al., 2013).

Beyond a mere delineation of the SC as a whole, objective methods based on high-resolution MRI to detect and describe the intra-collicular structure would be needed to fully understand its functional role in health and disease. A regular pattern characterizing the SC emerges from post-mortem studies describing the histology of the human SC (Laemle, 1980; Laemle, 1983; Tardif and Clarke, 2002; Tardif et al., 2005) as well as in non-human primates and the cat (Kanaseki and Sprague, 1974; Ma et al., 1990). Three main zones that constitute the superficial, the intermediate, and the deep SC with fundamental differences in their histology (May 2006), mirrored by differences in their functional MR signal (Loureiro et al., 2017; Katyal and Ress, 2014; Zhang et al., 2015), have been described. However, even finer subdivisions based on the intra-collicular structure can be made. When going from the surface of the SC towards its deeper parts, as many as seven layers with distinct microstructural features, alternating between myelinated fibers and neuronal cell bodies of different size and shape have been described (Kanaseki and Sprague, 1974; Ma et al., 1990). The use of quantitative MRI methods, performed with high-resolutions sequences and at high magnetic field strength, may be well suited to reveal this pattern, in virtue of their intrinsic sensitivity to cyto- and myeloarchitecture features of the SC (Nieuwenhuys et al., 2008).

In this study, our main objective was therefore to explore the possibility that high field, high-resolution MRI lends itself to the detection of the finer details of the SC, down to the level of single layers. We used relaxometry and QSM at 9.4T to examine anatomical properties of the human midbrain, in particular the SC and its internal structure in 14 subjects. Besides the SC, we also investigated the use of these different MR modalities in neighboring midbrain regions such as the RN, the cerebral aqueduct (CA) and a region covering white matter tracts in the central midbrain (WM), like the medial lemniscus and the ventral tegmental tract. We evaluated the MR-properties (R1, R2* and QSM) in these regions and calculated the coefficient-of-variation observed across subjects, both based on data from each subjects' individual images in native space and after transformation of all individual images into the common MNI brain space. Microstructural features were investigated by depth profiles (DP) across the SC layers, evaluated at different positions along the rostro-caudal axis, enabling the study of MR properties likely reflecting the underlying microarchitecture and the layering pattern of this structure. The combination of R1, R2*, and QSM maps provided a better understanding of the effect of the intrinsic microstructure, in terms of cyto- and myeloarchitecture of the SC tissue on the different MR maps than each single modality on its own. We foresee that the proposed approach can be used to improve our understanding of microstructural features of the SC layers and eventually relate these to their different functions.

Materials and methods

Participants

Fourteen healthy volunteers with a mean age of 27 years (range 21–34 years; 3 females) participated in this study. In accordance with local research ethics policies and procedures, the volunteers underwent a physical and psychological check-up by a local physician and provided written informed consent. All investigations were conducted in agreement with the Declaration of Helsinki in its most recent version (WMA, 2013).

Data acquisition and imaging protocol

All measurements were conducted with a 9.4T whole-body MRI scanner (Siemens, Erlangen, Germany), using an in-house-built head-coil with a 16-element dual row transmit array and a 31-element receive array (Shajan et al., 2014).

For each participant, we optimized the scanner parameters (static field homogeneity and transmit field) on a slice covering the midbrain prior to structural imaging. Mapping of the B1 field was made by the actual flip angle imaging method (AFI) (Yarnykh, 2007) with nominal flip angle FA = 60°; repetition time TR1/TR2 = 20/100 ms; echo time TE = 7 ms, voxel size = $3 \times 3 \times 5 mm^3$ and acquisition time TA = 3min45 s. We acquired four different sequences for mapping the midbrain: 1) a whole-brain MP2RAGE (Marques et al., 2010), inversion time TI1/TI2 = 900/3500 ms; FA = 4/6°; TR = 6 ms; volume TR = 9s; TE = 2.3 ms; 0.8 mm isotropic voxel size; GRAPPA = 3; partial Fourier factor PF = 6/8; and TA = 9min40s, which was used to calculate the T1 maps (Hagberg et al., 2017). 2) A 3D FLASH multi-echo sequence (ME FLASH), using mono-polar gradients with FA = 15°; TR = 41 ms; TE = 6–30ms in steps of 6 ms, 0.4 mm isotropic voxel size,