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Functional anatomy of the human thalamus at rest

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ABSTRACT

In the present work, we used resting state-fMRI to investigate the functional anatomy of the thalamus at rest by applying an Independent Component Analysis to delineate thalamic substructures into stable and reproducible parcels for the left and right thalamus. We determined 15 functionally distinct thalamic parcels, which differed in laterality and size but exhibited a correspondence with 18 cytoarchitectonally defined nuclei. We characterized their structural connectivity in determining DWI based cortical fiber pathways and found selected projections to different cortical areas. In contrast, the functional connections of these parcels were not confined to certain cortical areas or lobes. We, finally evaluated cortical projections and found particular subcortical and cortical pattern for each parcel, which partly exhibited a correspondence with the thalamo-cortical connectivity maps of the mouse.

Introduction

The thalamus is made up of a number of individual nuclei, which are closely connected to each other by association fibers and to cortical and subcortical brain regions by projection fibers. Almost all sensory, viscero- and somatosensory pathways, except olfactory afferences, project to the contralateral thalamus and are then forwarded to the cerebral cortex. The thalamus can, therefore, be seen as a central relay station and integration center of the CNS, which serves as the gateway to the telencephalon (Jones, 2007; Sherman and Guillery, 2006). The engaged substructures are commonly delineated by their cytoarchitectonic appearance using histochemical markers. Therefore, the number of reported nuclei varies with histological methods, although most cytoarchitecture studies identify 12–18 nuclei with several subdivisions of the individual nuclei (Morel, 2007; Nowinski, 2004; Schaltenbrand et al., 1977; Van Buren and Borke, 1972). All these atlases are still in use to identify and localize structures for neurosurgical or radiosurgical intervention, although they are only defined on the base of a small number of subjects.

However, recent neuroimaging technologies like diffusion-weighted imaging (DWI) and functional Magnetic Resonance Imaging (fMRI) offer novel insights into the structural and functional anatomy. Using DWI, a defined pattern of cortical connectivity can be determined by using probabilistic tractography methods (Behrens et al., 2003; Johansen-Berg et al., 2005a). This approach has successfully been used to identify the particular connection between the thalamus, cortical and subcortical areas and to parcellate the thalamus into distinct “connectivity-defined regions” (Jbabdi et al., 2009; Johansen-Berg et al., 2005a; Zhang et al., 2008a). Diffusion data have also been used to classify thalamic substructures using cluster analysis (O’Muircheartaigh et al., 2015, 2011; Wiegell et al., 2003; Ziyan and Westin, 2008) or to perform a spatial segmentation based on tensor orientation (Kumar et al., 2014; Mang et al., 2012; Unrath et al., 2008).

Similarly, resting state fMRI (r-fMRI) has been applied to either examine functional relations of cortical areas with the thalamus or to segregate thalamic subdivisions using an Independent Component Analysis (ICA) (Mezer et al., 2009; O’Muircheartaigh et al., 2015; Toulmin et al., 2015; Woodward et al., 2012; Yuan et al., 2015; Zhang et al., 2010). By applying ICA to the gray matter and a second-level ICA restricted to the basal ganglia and the thalamus, Kim and colleagues (Kim et al., 2013) identify 31 functional subunits according to their temporal activity patterns, which showed functional connectivity between hemispheres, between subdivisions of the basal ganglia and thalamus. In a recent comparison of functional segmentation of seed-based analysis and ICA approach Hale et al. reported that both whole brain analyzes resulted in plausible and comparable group-level thalamic subdivisions (Hale et al., 2015). However, a subsequent quantitative assessment of the spatial overlaps in comparison with a

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structurally-defined thalamic atlas revealed significant differences between both imaging results and post-mortem histology. Similar, O'Muircheartaigh et al. (2015) reported on a comparison of diffusion based thalamic parcellation with whole-brain resting state networks and concluded that both map to spatially distinct, and anatomically predictable networks in the same subjects. However, to achieve a tight correspondence, the authors had to reduce the variability in the functional connectivity patterns from 51 to a subset of 7 similar core network types.

In the present work, we intended to achieve a stable and unbiased functional parcellation of the human thalamus at rest. We used r-fMRI to estimate functionally distinct subdivisions of the thalamus by applying a modified ICA, which employs a preprocessing step, to better delineate the parcel similarity (van Oort et al., 2016). The achieved functionally distinct parcels were used to assess their size, laterality, correspondence with an available histology atlas (Krauth et al., 2010) and to examine their cortical projections using accessible diffusion and resting state data.

Material and methods

Volunteers

The magnetic resonance imaging (MRI) data of 40 age and gender balanced volunteers (20 male and 20 females; age 26–35 years, mean 31 years; s. Supplementary Table S1) were obtained with permission from the Human Connectome Project (HCP, Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657; (Van Essen, 2012). The data included structural, functional and diffusion MRI.

MR data specification

Structural imaging

T1w MPRAGE; TR 2400 ms; TE 2.14 ms; TI 1000 ms; Flip Angle 8°; Field of View (FOV) 224×224; 256 slices, voxel size 0.7 mm isotropic; Bandwidth 210 Hz/Px, IPAT 2; Acquisition time 7:40 min: sec.

r-fMRI (resting state fMRI)

Four sessions; multiband multi-slice-EPI (Moeller et al., 2010), 1200 scans/session, duration: 14:33 min, TR: 720 ms, TE: 33.1 ms, voxel size: 2 mm isotropic, 72 slices, multiband factor: 8.

***Diffusion Weighted Imaging** (DWI)*

DWI data were acquired by using a Spin-echo EPI sequence, TR: 5520 ms, TE: 89.5ms, flip angle; 78 degrees; voxel size: 1.25 mm isotropic, 111 slices, multiband factor: 3, echo spacing: 0.78 ms, b-values: 1000, 2000, and 3000 s/mm^2. For details, see: (Glasser et al., 2013; Van Essen, 2012).

r-fMRI preprocessing

HCP data were preprocessed (slice time correction, motion correction, co-registration, normalization to MNI 2 mm space) using the HCP pipeline (Fischl, 2012; Glasser et al., 2013; Jenkinson et al., 2012, 2002). Furthermore, FSL-Fix was used for data denoising, removing physiological nuisance effects as well as motion and multi-band artifacts. Data were finally smoothed with a 3.5 mm kernel.

Thalamic mask definition

The digital model of the 3-D anatomy of the thalamus according to the atlas of Morel was obtained by a written consent with Prof. G. Székely from the Computer Vision Laboratory of the ETH Zürich (Krauth et al., 2010). The mask was further realigned with thalamus connectivity based probability atlas available in FSL library (Behrens et al., 2003; Johansen-Berg et al., 2005a). The FSL thalamus probability atlas was thresholded to ensure that it only contains voxels inside the thalamus. The boundary of the thalamus mask was inspected visually on high-resolution T1-weighted scans by clinically experienced neuroradiologist (WG). The aligned transformation matrix was applied to each Morel thalamic nuclei to bring them into the MNI space.

Independent Component Analysis (ICA)

Functional parcellation was achieved using a multi-subject Group-ICA (FSL-MELODIC, (Beckmann and Smith, 2004) for the left and right thalamus separately (for detail s. Supplement Fig. S1). A group-ICA is performed on normalized fMRI data of four dimensional multi-subject's space without any additional step. In our analysis we employed a pre-processing before the ICA (van Oort et al., 2016), in which, first a spatial regression on resting state data against the thalamus anatomical mask was performed (resulting in average time courses per subject). Secondly a time course correlation the by means of an element-wise multiplication between the average thalamic time course and the time series of every voxel was calculated. These dynamic time courses are the temporally unfolded equivalent of Pearson correlations. Subsequently, a group-level ICA including the instantaneous correlation time series of every subject was performed. This approach parcellates the thalamus into sub-regions based on their temporal characteristics. Importantly, the dimensionality of the ICA was varied, and the split-half reproducibility across the population was calculated.

Split-half reproducibility analysis

In the split-half reproducibility analysis, subjects were randomly 20 times splitted into two equal size groups. Parcells were computed per split with ICA scale of 2 to 50. Furthermore, spatial overlap i.e. Dice's overlap was iteratively calculated for the resulting parcels at each ICA scale. The resulted spatial overlap matrices displayed a strong one-to-one match at on-diagonal indices between the parcels of each split. The reliability score for each ICA-scale was calculated by averaging the on-diagonal indices (s. Supplement Fig. 2a-b and Table S2) (van Oort et al., 2016). How many similar components or sources are in the data was estimated by using automatic model-order selection methods (Beckmann and Smith, 2004). The underlying idea behind the split-half reproducibility analysis was not to determine how many sources can be detected, but to assess how many sources can reliably and reproducibly be estimated. This approach resulted in a maximum reliability score for subdivision into 14–15 parcels for the right thalamus and 17 parcels for the left thalamus. We selected an equal number of 15 parcels for the right and left thalamus to allow hemispheric comparison and to examine their histological concordance and thalamo-cortical connectivity.

Lateralization and histological correspondence

Differences in parcel size and localization and between both hemispheres were compared as follows: the overlap of left thalamic parcels about the right thalamic parcels was determined by calculating the Dice coefficient, where the shared overlapping volume of both parcels was multiplied by two and then divided by the sum of both. The comparison with histology was first performed by calculating the Dice overlap of the right and left thalamic parcels with all 29 thalamic nuclei of the Morel atlas (Morel, 2007). However, in a second comparison we restricted the comparison to a set of 18 major nuclei by summarizing 16 smaller nuclei into 5 larger components: intralaminar nuclei (IL = CL, CM, Pf, sPf), midline nuclei (ML = CeM, Pv, MV), lateral nuclei (VPC = VPI, VPL, VPM), pulvinar nuclei (PU = PuA, Pul, PuL, PuM), and supragenicular and limitans nuclei (SG/Li = SG, Li), for which reported Dice coefficient could exceed 1. Importantly, in this compar-