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Validation of a protocol for manual segmentation of the thalamus on magnetic resonance imaging scans ☆

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ABSTRACT

We present a validated protocol for manual segmentation of the thalamus on T1-weighted magnetic resonance imaging (MRI) scans using brain image analysis software. The MRI scans of five normal control subjects were randomly selected from a larger cohort recruited from Lund University Hospital and Landskrona Hospital, Sweden. MRIs were performed using a 3.0T Philips MR scanner, with an eight-channel head coil, and high resolution images were acquired using a T1-weighted turbo field echo (T1 TFE) pulse sequence, with resulting voxel size $1 \times 1 \times 1$ mm^3. Manual segmentation of the left and right thalami and volume measurement was performed on 28–30 contiguous coronal slices, using ANALYZE 11.0 software. Reliability of image analysis was performed by measuring intra-class correlations between initial segmentation and random repeated segmentation of the left and right thalami (in total 10 thalami for segmentation); inter-rater reliability was measured using volumes obtained by two other experienced tracers. Intra-class correlations for two independent raters were 0.95 and 0.98; inter-class correlations between the expert rater and two independent raters were 0.92 and 0.98. We anticipate that mapping thalamic morphology in various neuropsychiatric disorders may yield clinically useful disease-specific biomarkers.

1. Introduction

"Essentially, the cortex must view the world through the thalamus; that is the only view the cortex has." (Sherman and Guillery, 2006)

1.1. Thalamic morphology in neuropsychiatric disorders using structural magnetic resonance imaging

Thalamic morphology has been investigated using structural magnetic resonance imaging (MRI) in a wide range of neuropsychiatric disorders. Meta-analyses have reported thalamic atrophy in schizophrenia (Konick and Friedman, 2001; Adriano et al., 2010) and major depressive disorder (Du et al., 2012), but not in bipolar disorder (Hallahan et al., 2011); increased thalamic volumes have been reported in patients with obsessive–compulsive disorder, with a reduction in volume in subjects treated with antidepressant medication (Gilbert et al., 2000; Atmaca et al., 2007). Thalamic atrophy has been reported both in sporadic Alzheimer's dementia (AD) (de Jong et al., 2008) and in the pre-symptomatic stage of familial AD (Lee et al., 2013; Ryan et al., 2013). Increasing thalamic atrophy has been reported in patients with progressive supranuclear

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palsy (PSP) enrolled in longitudinal studies (Whitwell et al., 2011); thalamic atrophy has also been observed in patients with frontotemporal dementia (FTD) (Cardenas et al., 2007; Chow et al., 2008) and Huntington's disease (HD) (Kassubek et al., 2005). Further investigating thalamic morphology may prove fruitful in enhancing disease etiology in the spectrum of neuropsychiatric disorders, and moreover could yield useful biomarkers with clinical utility.

1.2. Anatomical considerations of the thalamus for neuroimaging

Arising from the primitive forebrain (and sharing its origins with the telencephalon), the diencephalon can be broadly divided into the thalamus and hypothalamus, although its expanse encompasses a number of other structures (such as the habenular nuclei of the epithalamus). The thalamus can be divided into dorsal and ventral divisions: the dorsal thalamus is composed of nuclei having reciprocal connections with the cerebral cortex and striatum; despite having direct input from the cortex (and in part from the basal ganglia), the ventral thalamus does not generally project to the cortex (Jones, 2007). The ventral thalamus not only has an intimate functional relationship with the dorsal thalamus (see Zikopoulos and Barbas, 2007), but importantly its nuclei (such as the reticular thalamic nucleus and zona incerta) cloak the dorsal thalamus along the intercommissural distance, providing landmarks to assist with the challenge of lateral and inferior boundary definition of the dorsal thalamic mass on neuroimaging.

The dorsal thalamus is a paired structure, each roughly the size of a Brazil nut (*Bertholletia excelsa*) in humans. The thalami have a strategic central position in the brain which is readily identified on neuroimaging, being located at the base of each cerebral hemisphere respectively, between other subcortical structures and the cerebral cortex (Fig. 1). The two distinct dorsal thalami are found on either side of the third ventricle (which defines the thalamic medial boundary). Superiorly the thalami form the floor of the lateral ventricles for the greater part of their rostral-caudal extent. Laterally the dorsal thalamus is cloaked by the reticular thalamic nucleus (creating a fuzzy lateral boundary on MRI, by virtue of its reticulated or net-like appearance) and thence the internal capsule, ultimately separating the thalamus from the basal ganglia. Defining the inferior boundary is problematic throughout the rostro-caudal extent of the thalamus (until the pulvinar is reached), as there are a number of structures associated with the inferior boundary, including the zona incerta (of the ventral thalamus), substantia nigra, the subthalamic nucleus, the red nucleus, and hypothalamus for instance. A discerning feature of the inferior boundary is the presence of numerous white matter tracts surrounding these abovementioned structures; if these white matter tracts can be used to definitively exclude these structures from tracing, then one would have a more accurate description of the inferior dorsal thalamic boundary. Whilst the caudal pole of the thalamus is clearly defined by the emergence of the pulvinar, defining the rostral pole is perhaps the most challenging and would therefore support a caudal-rostral approach to tracing; the rostral pole requires careful tracing to exclude the hypothalamus, and to be traced in its entirety requires thin slices (e.g., ideally < 1.5 mm).

The internal organization of the dorsal thalamus can be conceptualized as having anterior, medial and lateral subdivisions, which are separated by a bowed sheet of myelinated fibers (the internal medullary lamina). Each of these subdivisions are composed of distinct thalamic nuclei, which are defined by characteristic cytoarchitecture and distinct patterns of connectivity, and their proposed involvement in distinct functional modalities (Table 1); of note, at least half of the thalamus is thought to be involved in cortico-cortical communication (the so-called higher order nuclei; see Table 1).

1.3. Development and utility of protocols for manual segmentation of the thalamus

A number of different approaches have been used in MRI to examine the thalamus, including image averaging (Andreasen et al., 1994) and edge-finding using anatomical templating (Buchsbaum et al., 1996). By virtue of having automated components, both of these approaches can be useful when dealing with large cohorts, but they can be problematic for precise boundary definition and accommodating individual variability between patients (for review, see Spinks et al., 2002), especially in the context of reported significant inter-individual variability of thalamic nuclei (Uylings et al., 2008). The region of interest approach is therefore the most reliable (albeit labor intensive) approach, involving a trained rater manually segmenting the thalamus in the MRI scan of each participant (Andreasen et al., 1990; Flaum et al., 1995; Gur et al., 1998, Portas et al., 1998; Spinks et al., 2002).

There are few widely available validated protocols for thalamic segmentation on MRI providing substantial anatomical detail for replication, and indeed addressing the key challenges of boundary definition. Perhaps the most widely cited is by Portas et al. (1998), who provide a description of the thalamus in 20–21 consecutive coronal 1.5 mm slices in a rostral–caudal direction; whilst the description of surrounding anatomical landmarks is thorough, there is little information regarding precise boundary definition (particularly the challenging lateral and inferior boundaries, and indeed the rostral pole of the thalamic mass). Spinks et al. (2002) describe an approach to manual segmentation of the thalamus and present 12 coronal 1.5 mm slices in their protocol, which they then used to train an artificial network for subsequent automated segmentation (with the goal of making large-scale studies more feasible); they appear to include the nuclei of the ventral thalamus. An advantage of their technique was the utilization of the tricolor image feature in BRAINS2 software, taking advantage of

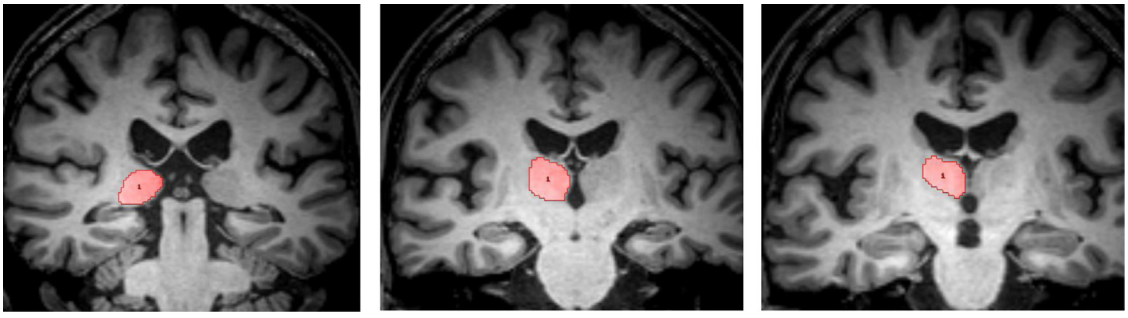

Fig. 1. Thalamic morphology in 3 slices in caudal-rostral progression on MRI scans (from left to right).

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