The thalamus as a putative biomarker in neuropsychiatry

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Abstract

Introduction

With a strategic central location between other subcortical structures and cortex, the thalamus is a pivotal hub in the subcortical connectome. Whilst the precise function of the thalamus is unclear, there is a growing body of literature unravelling its functional connectivity and potential involvement in a plethora of neuropsychiatric disorders. This article provides a brief overview of its functional neuroanatomy focusing on the dorsal thalamus, before presenting an overview of neuroimaging findings of thalamic morphology in a range of disorders, from schizophrenia and obsessive compulsive disorder, to various neurodegenerative disorders, such as Alzheimer’s dementia and progressive supranuclear palsy.

Conclusion

Mapping thalamic morphology in various neuropsychiatric disorders may provide important information regarding the onset, progression and, when disease-modifying agents are available, response to treatment.

Introduction

Clinical neuroanatomy of the thalamus

Development and gross anatomy

During development the primitive forebrain gives rise to the telencephalon (or end-brain, from which arise the cerebral cortex, striatum, amygdala, and associated structures) and the diencephalon (or between-brain, which gives rise to the thalamus and hypothalamus). Maturation of the thalamus and cortex are closely linked, such that a thalamic abnormality in the early neurodevelopmental period may impair normal cortical development (and vice versa) and, not surprisingly, thalamic pathology has been implicated in the neurobiology of schizophrenia.1 The neurodevelopment of the thalamus has been summarized extensively, and significant genetic factors have been identified.2,3 Further studies will be needed to ascertain whether genetic factors are associated with thalamic morphology, and hence provide the basis for putative endophenotypes in neuropsychiatric disorders.

The thalamus (from the Greek word thalamos, used to refer to an innermost room, storeroom, or bridal chamber) can be divided into dorsal and ventral divisions: the dorsal thalamus is composed of nuclei having reciprocal connections with the cerebral cortex and striatum, whereas the ventral thalamus does not generally project to the cortex.2 In humans, the dorsal thalamus is a paired structure, with a strategic central location between other subcortical structures and cortex. The two distinct dorsal thalami are located at the base of each cerebral hemisphere on either side of the third ventricle respectively (see Figure 1). The dorsal thalamus has anterior, medial and lateral subdivisions, defined by a curved sheet of myelinated fibres called the internal medullary lamina. These subdivisions are composed of distinct thalamic nuclei, based on cytoarchitecture, patterns of connectivity and functionality (see Table 1), however these nuclei share many features as outlined below.

Physiology

There are two types of neurons in dorsal thalamic nuclei which can be distinguished by their morphology and chemoarchitecture: locally acting GABAergic interneurons and glutamatergic relay cells projecting outside of the thalamus. The physiological properties of thalamic relay neurons indicate that they can undergo two main types of response modes which will determine the nature of the message relayed to the cortex: a burst response mode is thought to be utilized for signal detection, whereas a tonic response mode is believed to be utilized by the thalamic relay cells for more accurate signal analysis.4 It has been suggested that disruption of modulatory processes (i.e., shifting from signal analysis to signal detection) may lead to aberrant salience, such as that seen in schizophrenia.3

Drivers and modulators

The nuclei of the dorsal thalamus can be considered to receive two types of afferent fibres which are classified as either drivers or modulators, regardless of their origin (i.e., cortical or subcortical), and which can be defined on the basis of their synaptic morphology and post synaptic actions. In this sense, the drivers are essentially those afferents to the thalamus that carry the message to be passed on by the thalamocortical cells, whereas the modulators are those afferents to the thalamus that influence how this message is passed on by those thalamocortical cells.4

First order and higher order nuclei

Thalamic nuclei can be classified according to the afferents they receive. First order (or primary,) nuclei receive their drivers from a peripheral or subcortical structure, and receive modulators from pyramidal cells in layer VI of the ipsilateral cortex. In this scheme, visual, somatosensory and auditory afferents send peripheral sensory information to first order nuclei of the thalamus.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Nuclei</th>
<th>Principal inputs</th>
<th>Principal outputs</th>
<th>Proposed domain</th>
<th>functional domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific first order</td>
<td>anterior group</td>
<td>subiculum and presubiculum, mammillary nuclei</td>
<td>anterior limbic cortex, cingulate, subiculum, retrosplenial and presubiculum</td>
<td>limbic</td>
<td></td>
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<tr>
<td></td>
<td>lateral geniculate</td>
<td>retinal ganglion cells</td>
<td>visual cortex</td>
<td>vision</td>
<td></td>
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<tr>
<td></td>
<td>medial geniculate</td>
<td>inferior colliculus</td>
<td>auditory cortex of temporal lobe</td>
<td>hearing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ventral anterior</td>
<td>substantia nigra, deep cerebellar nuclei, vestibular nuclei, spinothalamic tract</td>
<td>motor and premotor cortices</td>
<td>motor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ventral lateral</td>
<td>globus pallidus, deep cerebellar nuclei, vestibular nuclei, spinothalamic tract</td>
<td>motor and premotor cortices</td>
<td>motor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ventral medial</td>
<td>substantia nigra, taste, vagal, spinal</td>
<td>diffuse, frontal, cingulate, primary somatosensory and gustatory, medial</td>
<td>integration of visceral-motor information</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ventral posterior</td>
<td>medial and trigeminal lemnisci, spinothalamic tract</td>
<td>primary and secondary somatosensory cortex</td>
<td>somatic sensation of body and face</td>
<td></td>
</tr>
<tr>
<td>Specific higher order</td>
<td>lateral posterior</td>
<td>parietal lobe, superior colliculus and pretectum</td>
<td>parietal lobe (area 5)</td>
<td>integration of sensory information</td>
<td></td>
</tr>
<tr>
<td></td>
<td>lateral dorsal</td>
<td>cingulate gyrus, fornix, pretectum, hypothalamus</td>
<td>cingulate gyrus, retrosplenial cortex</td>
<td>emotional expression</td>
<td></td>
</tr>
<tr>
<td></td>
<td>medial dorsal</td>
<td>amygdaloid nuclear complex, olfactory cortex, hypothalamus, spinal, superior colliculus</td>
<td>prefrontal cortex, including frontal eye field, orbitofrontal and lateral</td>
<td>limbic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>pulvinar</td>
<td>superior colliculus and pretectum, temporal, parietal and occipital lobes</td>
<td>temporal, parietal, occipital lobes (area 5, superior temporal gyrus) and prestriate cortex</td>
<td>integration of sensory information</td>
<td></td>
</tr>
<tr>
<td>Non-specific intralaminar</td>
<td>central lateral</td>
<td>spinothalamic, cerebellar nuclei, reticular formation, substantia nigra and</td>
<td>striatum, motor cortex, somatosensory cortex, parietal cortex, frontal cortex</td>
<td>arousal, eye movement, nociception</td>
<td></td>
</tr>
<tr>
<td></td>
<td>centre median</td>
<td>cerebellar nuclei, reticular formation, substantia nigra and superior colliculus</td>
<td>striatum, parietal and frontal cortex</td>
<td>as for central lateral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>parafascicular</td>
<td>periaqueductal grey, reticular formation</td>
<td>lateral, frontal cortex</td>
<td>as for central lateral</td>
<td></td>
</tr>
<tr>
<td>Non-specific midline</td>
<td>reunions</td>
<td>fornix</td>
<td>hippocampal formation and adjacent regions</td>
<td>limbic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>paratenial</td>
<td>?</td>
<td>medial frontal cortex</td>
<td>limbic</td>
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</table>
On the other hand, higher order (or association) nuclei receive their drivers from pyramidal cells in layer V of the ipsilateral cortex. In this scheme, higher order relays pass messages from one cortical area to another, regarding current output to motor or premotor centres from the driving cortical area, for instance. Just as sensory information passes through first order nuclei en route to cortex, so too corticocortical information passes through higher order nuclei (with direct corticocortical pathways providing some other function e.g., modulatory); this challenges the conventional view of corticocortical transmission. With regard to response mode of relay cells in higher order nuclei, it is thought that burst and tonic modes are utilized in a similar fashion: burst mode may be engaged to indicate a shift in the pattern of output in transthalamic corticocortical communication (from one cortical area to the other), and tonic mode then engaged by the higher order relay cells to transfer information more reliably to the other cortical area. Of note, research suggests there is more bursting in higher order nuclei than in first order relays. Although limited, current evidence suggests that drivers to higher order relays come from several different cortical areas, suggesting the relay is likely to represent several different functions. Whilst their precise function remains elusive, what is clear from the study of the higher order nuclei is that at least half of the thalamus is dedicated to transthalamic corticocortical communication, with the implication that disruption of this type of signaling could impact on higher cortical functions. Indeed, the role of the thalamus in perceptual processing is likely to be significant: Sherman and Guillery speculate that a function of thalamocortical inputs to cortex (either first order or higher order) could be to keep the cortex updated on the most recent motor commands.

**Topographical organization of the thalamus**

Many of the afferent and efferent connections of the thalamus are mapped, including driver afferents to first order nuclei, as well as topographically organized first and higher order thalamocortical and corticothalamic pathways. Trans-synaptic neurodegeneration has been proposed as a mechanism in neurodegenerative disease whereby deafferentation from cortical neurons can lead to synaptic dysfunction and hence neuronal spread of disease along vulnerable neural networks. This could be one mechanism that leads to subcortical pathology such as neuronal loss in neurodegenerative disease, as evidenced in the striatum in Huntington’s disease (HD), frontotemporal dementia (FTD) and Alzheimer’s disease (AD). Given the topographical relationship of thalamus to cortex, one would predict that the thalamus could serve as a map of structural change in the cortical afferent pathways in various neurodegenerative conditions.

**The thalamus as a critical hub in the subcortical connectome**

From a neural circuit perspective, there are a number of well-defined anatomical loops involving the thalamus in addition to those already described. For instance, frontostriatal-thalamocortical circuits are thought to form the main network by which motor activity and behaviour in humans is mediated, and may explain the similarity of behavioural changes in frontal cortical and subcortical disorders. The thalamus is a critical hub in these networks, as it is proposed that cortico-subcortical lesions in neurodegenerative disease may disconnect these circuits, and this underpins the manifest neuropsychiatric dysfunction, such as cognitive and behavioural disturbances seen in FTD for instance. Similarly, dysfunction of cerebello-thalamocortical pathways have also been linked to neuropsychiatric disease. Andreasen and colleagues have reported that disruption of neural circuits linking the cortex, thalamus and cerebellum may be at play in schizophrenia, speculating that disruption of this circuitry may underpin emotional and cognitive dysfunction. As a pivotal structure in the subcortical connectome, further investigation of the thalamus is likely to be fruitful in various neuropsychiatric disorders.
Thalamic function and dysfunction

With the exclusive exception of most olfactory inputs, all sensory pathways on route to the cerebral cortex first pass through the dorsal thalamus. It was thought that the function of the dorsal thalamus extended no further than relaying information, and indeed it has been described as the “gateway” to the cortex. In terms of a current conceptualization of thalamic function, the thalamic relay is thought to function as a modulatory gate (rather than an integrator of a number of messages) with its component relay cells passing the message from their driving afferent (be it cortical or subcortical) to the cortex; signalling occurs either in burst or tonic modes, albeit with slight modifications. Whilst it is not entirely clear what advantage is subserved by sending information through the thalamus before it reaches a cortical area, this will be pivotal in understanding the thalamus.4 In conceptualizing the role of the thalamus in neuropsychiatric disorders, it will be useful to consider a failure of neural circuitry involving the thalamus, rather than neuropsychiatric symptoms arising directly from the thalamus itself. The role of thalamic pathology in the disease state could then be considered a failure of its relay functions or an abnormality of gating that acts on the messages it receives. The aim of this critical review was to discuss the thalamus as a putative biomarker in neuropsychiatry.

**Discussion**

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

**Thalamic morphology in psychiatric disorders using structural MRI**

The following section offers a concise overview of some of the findings of thalamic morphology using structural MRI in a range of psychotic, mood and anxiety disorders; given the constraints of space, data pertaining to functional MRI and diffusion tensor imaging (DTI) in these disorders is beyond the scope of this overview.

A comprehensive review of thalamic anomalies in schizophrenia has been provided by Byrne and colleagues.1 A meta-analysis by Konick and Friedman 12 suggests a volume deficit of the thalamus relative to brain size in schizophrenia, and thalamic size has been demonstrated to correlate inversely with symptom severity.16 Thalamic volume deficit has been reported in first-episode psychosis, medication-naive patients with schizophrenia, as well as those patients who were taking antipsychotic medication, and there is conflicting data regarding thalamic volume increases with antipsychotic medications.1,15,17 The majority of thalamic volume deficit in schizophrenia involves primarily two thalamic nuclei, namely the medial dorsal thalamic nucleus (MD) and the pulvinar, which relate to prefrontal and temporal cortices. The medial dorsal nucleus (its efferent fibres targeting the prefrontal cortex in a topographical manner) has received particular attention in schizophrenia, with consistent reports of bilateral volume reduction in MD relative to healthy controls;18 similarly bilateral volume deficits have been reported in the pulvinar.18,19 An MRI study in 46 individuals with early-onset psychosis and 34 healthy controls supported these findings, and revealed a regional reduction in thalamic volumes between groups (most significant in the right anterior MD area and pulvinar).19 Gaser and colleagues 20 argue that thalamic shrinkage (in the regions corresponding to MD and the pulvinar) appears to be an important determinant of ventriculomegaly in patients with schizophrenia, rather than diffuse brain atrophy.

Disparate findings regarding thalamic morphology have been reported in mood disorders, with a ‘mega-analysis’ of 321 patients with bipolar affective disorder (type 1) reporting no variation in thalamic volumes compared with controls,21 and a meta-analysis of 20 voxel-based morphometry studies in major depressive disorder involving 543 patients and 750 controls supporting reduced thalamic volumes in patients with depression.22 Thalamic volume has been reported as increased bilaterally in medication-naive patients with obsessive compulsive disorder (OCD) in child and adult populations, and a reduction in thalamic volume reported following antidepressant treatment.23,24 There is sparse information of thalamic morphology in other anxiety disorders, which may in part reflect the very distinctive morphological findings in OCD compared with other anxiety disorders as reported in a recent meta-analysis.25 Whilst structural MRI in psychiatric conditions has limited clinical utility at the present time, for the time being it continues to yield important information that enhances our etiological understanding of disease from a brain structural basis.

**Thalamic morphology in neurodegenerative disorders using MRI**

The majority of neuroimaging studies in the common neurodegenerative disorders have focused on dysfunctional neocortical networks in the common neurodegenerative disorders, most likely because of the crucial roles of neocortex in higher cortical functions. There is a growing body of literature identifying the role of important subcortical structures in these networks, such as the striatum in AD, behavioural variant FTD, progressive nonfluent aphasia and stroke.10,26,27,28,29 Relatively few studies have investigated thalamic morphology in the neurodegenerative disorders. In familial AD, thalamic atrophy has been reported in the pre-symptomatic stage of disease,20 and thalamic atrophy...
has been reported in sporadic AD relative to controls.\textsuperscript{26} Further, thalamic atrophy in AD is associated independently with cognitive deterioration, controlling for age, gender, educational level, intracranial volume and neocortical grey matter volume.\textsuperscript{24} Longitudinal studies of thalamic morphology in AD are warranted. Thalamic atrophy on MRI has been reported in cohorts with progressive supranuclear palsy (PSP) relative to controls, but not in patients with Parkinson’s disease (PD), multisystem atrophy, cortico-basal degeneration (CBD), or dementia with Lewy bodies (DLB).\textsuperscript{31,32,33,34,35} In a multi-modal approach, Whitwell and colleagues\textsuperscript{35} reported atrophy in the thalamus in PSP using MRI and reduced thalamic functional connectivity using fMRI relative to controls, with DTI data implicating the ventrolateral (or motor) thalamus. Using DTI and structural MRI, thalamic atrophy has been reported early in the disease stages of PSP primarily affecting the pulvinar, medial dorsal and anterior nuclei,\textsuperscript{26} and using serial MRIs at 6 month intervals, progressive thalamic atrophy over time relative to controls has also been reported.\textsuperscript{35} The morphology of the thalamus might thus be a useful biomarker in PSP. Significant atrophy has been reported in the thalamus of patients with FTD compared with controls,\textsuperscript{37} however it is yet to be determined how thalamic morphology relates to the specific pathological subtypes of this heterogeneous condition, and this requires further investigation. Thalamic atrophy has been associated with cognitive deterioration (but not other clinical features, such as motor function) in early stages of HD relative to controls; symmetrical atrophy in the regions of the medial dorsal nucleus, and the ventral lateral and intralaminar nuclear groups were reported.\textsuperscript{38} Further investigation of thalamic morphology is warranted in HD, together with longitudinal data if indicated.

**Future directions**

Further studies are required to investigate how the morphology (shape and volume) of the thalamus is relevant to and indicative of the integrity of neural circuits subserving cognition, emotion, movement and behaviour. From a clinical perspective, correlation of these clinical features (e.g., cognitive or emotional disturbance, or movement disorder) with thalamic morphology will provide a better understanding of the neurobiology of neuropsychiatric conditions, and potentially yield clinically useful biomarkers. Further, determining whether genetic factors are associated with thalamic volume may provide a genetic basis for an endophenotype, and hence provide putative endophenotypes in neuropsychiatric disorders.

Whilst the significance of altered thalamic morphology in schizophrenia, depressive disorders and OCD is yet to be determined, further studies are warranted. For instance, investigating for an association between thalamic atrophy and cognitive dysfunction in schizophrenia may be fruitful, particularly in patients enrolled in genome wide association studies. Whilst structural MRI in these conditions has limited clinical utility at the present time, it has the potential to advance our etiological understanding of psychiatric disease from a brain structural basis. Preliminary data in the neurodegenerative disorders suggests that investigating thalamic morphology is likely to yield biomarkers for these disorders. Most age-related neurodegenerative disorders are characterized not only by abnormal folding and accumulation of disease-specific proteins, but also progressive pathological changes that occur in anatomical patterns that are characteristic of a particular dementia (which likely underpins the characteristic clinical syndromes for different dementias). The conceptualization of the dementias on a neural circuit basis suggests that these abnormal proteins take seed in a particular part of the nervous system and then migrate along the brain’s intrinsic pathways over time, affecting through a plethora of mechanisms both cortical and subcortical structures.\textsuperscript{14} Hence, as a pivotal structure in the subcortical connectome, it is not surprising that altered thalamic morphology has been identified in AD, PSP and FTD, and possibly HD.

**Conclusion**

Mapping thalamic morphology in neuropsychiatric disease may provide important information regarding the onset, progression and ultimately (when disease-modifying agents are available), treatment response in a form directly related to neuropsychiatric dysfunction.

**Acknowledgement**

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All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript. All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

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