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Morphometric analysis of thalamic volume in progressive supranuclear palsy: In vivo evidence of regionally specific bilateral thalamic atrophy☆

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ABSTRACT

We investigated whether differences were detectable in the volume and shape of the dorsal thalamus on magnetic resonance imaging in patients with progressive supranuclear palsy (PSP). Manual segmentation of the left and right thalami on magnetic resonance imaging scans occurred in 22 patients with clinically diagnosed PSP and 23 healthy controls; thalamic volumes (left, right, total) were calculated. Between group differences were explored by multivariate analysis of co-variance, using age and intracranial volume as covariates. Analysis of the shape of the thalamus was performed using the spherical harmonic point distribution method software package. Patients with PSP were found to have significant bilateral thalamic atrophy on magnetic resonance imaging; there was significant shape deflation over the anterior-lateral and anterior-ventral surfaces bilaterally, and over the right caudal thalamus. Recognizing decreased thalamic morphology in PSP patients in vivo may be an important component of an ensemble of diagnostic biomarkers in the future, particularly given the difficulty of distinguishing PSP from other Parkinsonian conditions early in the disease course.

1. Introduction

Progressive supranuclear palsy (PSP) is a neurodegenerative disorder with a neuropsychiatric presentation leading rapidly to disablement and death; prevalence reports vary from 1 to 5 per 100,000 (Nath et al., 2001; Shi et al., 2013), with an increasing incidence with age [1.7 cases per 100,000 at ages 50–59 years; 14.7 cases per 100,000 at ages 80 and 99 (Litvan, 2003)]. In PSP (Williams and Lees, 2009): the mean age of onset is 65 years, with most patients becoming dependent on care within 3–4 years of presentation, and with death generally occurring within 6–12 years from diagnosis (Williams and Lees, 2009; Williams and Litvan, 2013). Whilst PSP shares many features with other Parkinsonian conditions (such as bradykinesia, rigidity and postural instability), it is characterized clinically by the presence of additional motor, cognitive and behavioural features (e.g., vertical supranuclear gaze palsy; dysarthria, dysphagia, executive dysfunction; decreased verbal fluency, disinhibition; apathy; mood and anxiety symptoms; dementia) (Steele et al., 1964; Willams and Lees, 2009). The early clinical features of the disease, however, are often subtle and can be difficult to distinguish from other conditions such as idiopathic Parkinson's disease (PD), corticobasal degeneration, dementia with Lewy bodies, multiple system atrophy (MSA), and vascular Parkinson-

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ism (Williams and Lees, 2009). Whilst there are currently no reliable diagnostic biomarkers for PSP (and thus accurate diagnosis depends on clinical acumen), in recent years there has been considerable interest in the use of neuroimaging modalities to understand morphological changes and circuit disruption in PSP and the clinical correlates thereof, towards not only a better understanding of disease aetiology, but also towards aiding in early diagnosis and prognostication (Shi et al., 2013). Invariably, once disease modifying agents become available, neuroimaging in PSP may also provide both surrogate treatment endpoints and a means to monitor treatment response.

Most age-related neurodegenerative disorders are characterized by the abnormal folding and accumulation of proteopathic agents: PSP is a primary tauopathy, and microscopic features of the disease include the deposition of tau protein in neurons and glia, forming globose neurofibrillary tangles and star-shaped astrocyte tufts (Williams and Lees, 2009; Boxer et al., 2006). From a microscopic perspective, neuronal loss and gliosis are seen particularly in the basal ganglia, thalamus, striatum and brainstem (Dickson et al., 2007; Henderson et al., 2000). Macroscopic atrophy of the frontal cortex can be observed on magnetic resonance imaging (MRI), together with atrophy of a number of key subcortical structures, including the thalamus (Shi et al., 2013; Boxer et al., 2006; Messina et al., 2011), mesencephalon and striatum (Looi et al., 2011) and dentatorubrothalamic tract which runs through the superior cerebellar peduncles (Whitwell et al., 2011; Josephs et al., 2013; Surova et al., 2015). Taken together, these findings could suggest disease involvement of the key structures and circuitry of the subcortical connectome (specifically the corticostriatal-thalamocortical and corticocerebellar circuits) may underpin the neuropsychiatric clinical features of PSP (Looi et al., 2014a; Power and Looi, 2015).

There have been a small number of previous studies exploring the changes in the thalamus in patients with PSP. A small post mortem study found no significant difference in the total volume of the thalamus in PSP patients compared with controls, however they identified prominent cell loss in the caudal intralaminar and centromedian nuclei of the thalamus (Henderson et al., 2000). A number of MRI studies utilizing automated segmentation techniques have subsequently reported thalamic atrophy in patients with PSP relative to controls (Price et al., 2004; Boxer et al., 2006; Messina et al., 2011; Hess et al., 2014). Furthermore, a number of notable multimodal studies have attempted to better define the pattern of thalamic atrophy in PSP: using diffusion tensor imaging (DTI) and structural MRI (VBM study), thalamic atrophy has been reported to involve the pulvinar, mediodorsal thalamic nucleus and anterior thalamic nucleus bilaterally (Padovani et al., 2006); and using resting state functional MRI (fMRI), DTI and structural MRI, reduced thalamic functional connectivity was reported, with DTI data implicating the ventral lateral (or motor) thalamus (Whitwell et al., 2011). In addition, longitudinal MRI studies using automated segmentation techniques show that the thalamus undergoes progressive atrophy over time in PSP (Whitwell et al., 2012).

Few if any studies have utilized manual segmentation techniques and morphological analysis of the thalamus in patients with PSP. The most commonly used method to identify the volume of the thalamus is the manual Region of Interest (ROI) approach on MRI, which provides a highly reliable method and allows for inter-individual variability of thalamic morphology (Hess et al., 2014; Spinks et al., 2002). This method involves the manual tracing of the boundaries of a region in the brain on consecutive slices, which are then merged to calculate the volume of the structure (Scorzin et al., 2008). The ROI method is time consuming and requires a trained operator with consistent technique and skill; it is therefore difficult to use in large studies, however for a small sample size it provides the greatest reliability (Spinks et al., 2002).

Our research network - the Australian, United States, Scandinavian, Spanish Imaging Exchange (AUSSIE) - has been focused upon the role of primarily subcortical recurrent neural circuits in the human central nervous system as structural and functional bases of clinical features of neurodegenerative disease (Looi et al., 2014b). To date, using advanced magnetic resonance imaging analysis of the morphology of the striatum, we have demonstrated that regional atrophy of the surface correspondence of the afferents of the striatum relating to specific recurrent cortico-striato-thalamic circuits, is correlated with clinical measures of cognition, motor and behavioural changes in age-related white matter change (Looi and Walterfang, 2013; Macfarlane et al., 2013, 2015a), and in behavioural variant frontotemporal dementia (Macfarlane et al., 2015b).

We have hypothesized that the dorsal thalamus, as a key component of recurrent cortico-striato-thalamo-cerebellar circuits may analogously be affected in neurodegenerative disease such as PSP (Power and Looi, 2015). If specific topographic atrophy of the surface of the thalamus, relevant to the nuclei of the thalamus, can be demonstrated in PSP compared to healthy controls, then a neural structural basis for correlation with clinical features when such data is available, constituting a potential endomorphotype (intermediate morphotype) may be developed (Power and Looi, 2015). This may lead to possible endophenotypes based upon the function of the recurrent cortico-striato-thalamo-cerebellar circuits traversing the thalamus.

The primary aim of this study was to use manual ROI analysis to determine if differences are detectable in the volume of the dorsal thalamus on MRI scans of those with PSP relative to healthy controls in a group with a moderate sample size in comparison to previous studies (Hess et al., 2014); in addition, to determine if these morphological changes were detectable at the early (within 4 years of symptom onset) rather than later stages of disease. Based on previous studies, we hypothesized that patients suffering from PSP would have regionally specific (i.e. potentially related to at least surface afferent and efferent topographic representations of the structures) bilateral thalamic atrophy relative to healthy controls.

2. Methods

2.1. Subjects

Twenty-two patients with PSP and twenty-three healthy controls were recruited for the study from Lund University Hospital and Landskrona Hospital, Sweden (Table 1). The diagnosis of PSP was made using established clinical criteria as described by Litvan in combination with clinical investigations (Litvan et al., 2003): 3 patients had possible PSP; 14 patients had probable PSP; and 5 patients had definite PSP. Fifteen of the patients and controls were analyzed in a previous study of the striatum (Looi et al., 2011). MRI scans for all patients were performed within 4 years of symptom onset. Ethical approval was obtained for the study from the Regional Ethical Review Board, Lund, Sweden and the Australian National University.

Table 1
Demographic details for the two groups.

	Group	Number	Mean (Standard Deviation)	Difference (*p*-value)
Age at study (years)	PSP	22	68.05 (6.52)	0.32*
	Control	23	65.22 (11.69)	
Sex	PSP (M:F)	9:13		0.39§
	Control (M:F)	13:10		0.53§
ICV	PSP	22	1465.71 (214.21) mm^3	0.614*
	Control	23	1438.40 (134.44) mm^3	

* *p*-value from independent samples *t*-test, no assumption of equal variance.
§ obtained by Chi-square test for independence; ICV = intracranial volume; M:F = male-to-female ratio; PSP = progressive supranuclear palsy.