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Characterisation of meta-analytical functional connectivity in progressive supranuclear palsy

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AIM: To characterise the meta-analytical functional connectivity patterns in progressive supranuclear palsy (PSP) and compare them to idiopathic Parkinson's disease (IPD).

MATERIALS AND METHODS: It was previously reported that PSP and IPD showed distinct regions of brain atrophy based on voxel-based morphometry (VBM) meta-analysis. Using these regions as seeds, healthy control data were referenced to create and statistically compare meta-analytical functional connectivity maps of PSP and IPD.

RESULTS: Some overlap was noted between the two diseases, including within the thalamus, striatum, and prefrontal cortex; however, the PSP seeds demonstrated more extensive functional co-activity throughout the brain, particularly within the midbrain, precentral gyrus, parietal cortex, basal ganglia, and cerebellum.

CONCLUSION: These findings may help guide future longitudinal studies in the development of new functional imaging biomarkers for diagnosis and assessing treatment response.

Introduction

Progressive supranuclear palsy (PSP) is a neurodegenerative tauopathy associated with neurofibrillary tangles and ballooned argyrophilic neuronal degeneration in the basal ganglia, brainstem, and frontal lobes.[1] Patients classically present with Parkinsonian features, followed by the development of vertical gaze palsies, postural instability, dysarthria, and cognitive impairment.[2] Compared with idiopathic Parkinson's disease (IPD), those afflicted with PSP deteriorate more rapidly (mean survival of 8 versus 15 years), and show little response to levodopa and deep brain stimulation therapy.[3] In lieu of these clinical differences, as well as the necessity of appropriately assigning patients in clinical trials, distinguishing these diseases is of great importance.

Although clinical criteria exist, the diagnosis of PSP can be challenging especially in early-stage disease. Structural neuroimaging has shown promise as a diagnostic tool, including manual measurements and semi-automated techniques such as voxel-based morphometry (VBM).[4,5] Regions of atrophy have been reported within the thalamus, midbrain, striatum, superior cerebellar peduncles, and pre-frontal cortex (PFC)[6,7]; however, a potential limitation of this approach is that atrophy may not be apparent

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in early and pre-clinical disease.[8] Additionally, the significance of these findings and their relationship with clinical impairment remains to be elucidated.[9]

An alternative approach is to focus on the relationship between different brain regions, with an interest in changes to the underlying connectivity. Structural connectivity, representing integrity of white matter tracks, may be evaluated with diffusion imaging, whereas functional connectivity can be assessed through functional MRI (fMRI). Along these lines, there is growing opinion that neurodegenerative disorders, including PSP, may be characterised using a network-based paradigm.[10]

Coordinate-based neuroimaging meta-analyses represent a rapidly evolving field, and has been applied to VBM as well as fMRI datasets.[11–13] As the number of peer-reviewed publications has grown, so has the statistical power of this analytical approach. This has made it possible to identify co-activation patterns across a large number of studies, deriving a meta-analysis of functional connectivity for a user-specified region of interest. A VBM meta-analysis recently reported characteristic atrophy patterns in PSP and IPD.[14] The next step towards defining a robust imaging biomarker for PSP is to evaluate the functional connectivity of these atrophy regions and how these co-activation profiles differ between PSP and IPD. The purpose of the present study was to (1) determine the meta-analytical functional co-activation patterns of the VBM meta-analysis results for PSP and (2) to contrast these co-activation patterns with those of IPD.

Materials and methods

Institutional review board approval was waived as no identifying information or primary patient data were acquired for this study.

Meta-analytical connectivity modelling (MACM)

MACM is based on the concept that whole-brain activation patterns across studies can identify regions with above-chance covariance. This is similar to resting state fMRI (rsfMRI), which uses temporal co-variations in regional activation to detect functional connectivity.[13,15,16] In MACM, consistent co-activations between two separate brain regions across different fMRI studies may be thought of as the meta-analytical correlate of functional connectivity.[17] This approach overcomes some of the challenges facing individual task-based fMRI studies, including task specificity, low signal-to-noise ratio, and competing network activities.

First, seed regions were derived based on previous VBM meta-analysis of grey matter atrophy in PSP and IPD.[14] This included the left inferior frontal gyrus (IFG), thalamus, midbrain, insula, left claustrum, anterior cingulate cortex (ACC), and left caudate body for PSP. For IPD, these included the bilateral IFGs, left medial frontal gyrus, left superior temporal gyrus, and right middle frontal gyrus (MFG). A search was then conducted of the BrainMap database (which stores coordinate-based results of over 13,000 fMRI experiments) for whole-brain task-based fMRI experiments in healthy subjects demonstrating activations within the seed regions.[18,19] To avoid pre-selection bias and enable a data-driven approach, all eligible studies were considered regardless of behavioural categories.

Activation likelihood estimation (ALE) meta-analyses were then performed on the coordinates that were identified as co-activating with the seed regions using GingerALE (version 2.3.2). As previously described, the ALE method determines the above-chance convergence between studies, which can be generalised to experiments outside of the current analysis.[12,14] A cluster-level threshold $p<0.05$ was incorporated, along with a permutation threshold of 1,000 and false discovery rate (FDR) of $pN<0.05$, to generate MACM-ALE maps of significant convergence across the BrainMap foci.

To facilitate spatial comparisons of IPD and PSP co-activation patterns, the resultant MACM-ALE images were first transformed into binary data using Mango software.[19] A summarised MACM colour map was then generated, demonstrating the extent to which connectivity was shared among the seed regions for each condition. A different colour was attributed to each voxel value (range 0–7). Anatomical labels were assigned based on the Tailarach Daemon in Mango, and the results were overlaid on a standardised T1-weighted brain template for visualisation (Colin 27 Average Brain).[20]

Contrast analysis

To quantitatively contrast the functional connectivity of PSP to IPD, firstly, separate co-activation maps were generated from the combined seeds of each condition. Next, the voxel-wise differences in ALE scores for the respective MACM maps were calculated. The experiments contributing to either analysis were then pooled and randomly divided into two groups of the same size as the set of contrasted experiments.[12] The voxel-wise ALE scores for these randomly assembled groups were subtracted from one another and recorded. Repeating this process over 10,000 permutations yielded a null distribution of ALE-score differences between PSP and IPD, after which *p*-values and *Z*-scores were obtained. A map of true differences was then derived using a voxel-wise family-wise error (FWE) threshold of 0.01.

Conjunction analysis

In order to identify consistent functional connectivity maps showing co-activations in both PSP and IPD, conjunction analyses were performed between the two conditions. For this purpose, the thresholded voxel-wise FWE of 0.01 was calculated for each condition, and the intersection between the connectivity maps of both analyses was found to identify areas with significant shared functional co-activity.

Results

MACM of consistent atrophy in PSP

MACM was performed for each of the PSP atrophy seeds (Fig 1; Electronic Supplementary Material Table S1). The

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