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Lewy body compared with Alzheimer dementia is associated with decreased functional connectivity in resting state networks

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ABSTRACT

Resting state functional magnetic resonance imaging (fMRI) was used to measure whole brain functional connectivity within specific networks hypothesised to be more affected in dementia with Lewy bodies (DLB) (a disease characterised by prominent attentional deficits, spontaneous motor features of parkinsonism and depression) than in Alzheimer's disease (AD) and controls. This study involved 68 subjects (15 DLB, 13 AD and 40 controls) who were scanned using resting state BOLD (blood-oxygen-level-dependent) fMRI on a 3 T MRI scanner. Functional connectivity was measured using a model-free independent component analysis approach that consisted of temporally concatenating the resting state fMRI data of all study subjects and investigating group differences using a back-reconstruction procedure. Resting state functional connectivity was affected in the default mode, salience, executive and basal ganglia networks in DLB subjects compared with AD and controls. Functional connectivity was lower in DLB compared with AD and controls in these networks, except for the basal ganglia network, where connectivity was greater in DLB. No resting state networks showed less connectivity in AD compared with DLB or controls. Our results suggest that functional connectivity of resting state networks can identify differences between DLB and AD subjects that may help to explain why DLB subjects have more frequent attentional deficits, parkinsonian symptoms, and depression than those with AD.

1. Introduction

Dementia with Lewy bodies (DLB) is the second most common cause of neurodegenerative dementia after Alzheimer's disease (AD) (McKeith et al., 1996, 2005; Geser et al., 2005). The clinical symptoms of DLB and AD can overlap, a fact that makes differentiating the disorders difficult. Neuroimaging is used in dementia to better understand neurobiological changes underpinning key symptoms and clinically to enhance diagnostic accuracy. Compared with the literature on AD, few neuroimaging studies have investigated DLB, and the neural changes responsible for the distressing symptoms of attentional deficits, motor features of parkinsonism, and depression that are characteristic of DLB are not well understood.

Resting state BOLD (blood-oxygen-level-dependent) functional magnetic resonance imaging (fMRI) shows temporal correlations in spontaneous low-frequency fluctuations (SLFs) (at < 0.1 Hz) between distant but anatomically connected brain regions (Biswal et al., 1995), representing functional connectivity (Fox and Raichle, 2007). Both independent component analysis (ICA) (Beckmann et al., 2005) and seed-region (Damoiseaux et al., 2006) approaches can be used to organise brain regions into at least 10 resting state networks that plausibly represent different sensory and cognitive processes.

Initially, resting state fMRI studies focussed on the default mode network (composed of posterior cingulate, precuneus, lateral parietal, lateral temporal and medial frontal regions), which is active at rest and deactivates when a task is performed (Raichle et al., 2001). This network has been shown to be affected in AD, with abnormalities increasing as the disease progresses (Zhou et al., 2010; Zhang et al., 2011; Damoiseaux et al., 2012), but more recently it has been shown that other resting state networks are also affected in AD, for example, the sensory motor, dorsal attention and salience networks (Brier et al., 2012; Zhou et al., 2010). Few studies have investigated functional connectivity in DLB, and those studies which have considered this group have used slightly different analytical approaches and, perhaps as a consequence, came to different conclusions.

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Previously, we investigated functional connectivity in DLB and AD using a seed-region approach and showed abnormally increased connectivity compared with findings in controls in the posterior cingulate and putamen in DLB, in the hippocampus in AD, and in the caudate and thalamus in both DLB and AD (Kenny et al., 2011, 2013). Galvin et al. (2011) used a similar approach but focussed solely on precuneus connectivity and used the whole structure as the seed region. Their study showed both increased connectivity with putamen and parietal regions and decreased connectivity with prefrontal and primary visual cortices (Galvin et al., 2011).

In the current study, instead of measuring connectivity with predefined regions of interest, we adopted a model-free independent component analysis (ICA) approach. This approach enables investigation of whole brain functional connectivity ensuring optimal use of the study data. The ICA method was used in DLB subjects by Franciotti et al. (2012), who reported no abnormalities in default mode network connectivity in DLB but did not report analysis of other identified networks (Franciotti et al., 2012). Here we investigated the wider set of resting state networks in DLB subjects. We hypothesised that functional connectivity would be significantly altered in DLB compared with control and AD subjects within the following networks:

(a) Default mode, salience and executive networks because of the attentional deficits which are greater in DLB than AD subjects (Ballard et al., 2001).
(b) Basal ganglia and limbic networks, specifically the caudate because of its role in emotional regulation and the greater severity of depression in DLB, the putamen because structural pathology and neurotransmitter abnormalities here are associated with parkinsonian symptoms in DLB (Walker et al., 2002; O'Brien et al., 2004), and the thalamus which is involved in maintaining consciousness (Perry and Perry, 2004) and fluctuating cognition is a core feature of DLB (McKeith et al., 1996).

2. Methods

2.1. Participants

This study involved 68 subjects aged over 60 years: 15 DLB, 13 AD and 40 control subjects; the same subjects have also been investigated in previous studies (Kenny et al., 2010, 2011, 2013). DLB and AD subjects were recruited from clinical Old Age Psychiatry, Geriatric Medicine and Neurology outpatient services; controls were recruited through local advertisement or were partners of the dementia subjects. The study was approved by the local ethics committee, and all subjects gave signed informed consent for participation. DLB subjects met consensus criteria for probable DLB including the presence of two or more core clinical features (fluctuating cognition, visual hallucinations and/or parkinsonism) (McKeith et al., 1996, 2005). AD subjects fulfilled National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable AD (McKhann et al., 1984). Diagnoses were made by consensus between two experienced clinicians, a method previously validated against autopsy diagnosis (McKeith et al., 2000). All of the DLB subjects who underwent ^{123}I-labelled *N*-(3-fluoropropyl)-2ß-carbomethoxy-3ß-(4-iodophenyl) nortropane (^{123}I-FP-CIT) single photon emission computed tomography (SPECT) imaging during their clinical diagnostic assessment ($n=9$) showed reduced dopamine transporter uptake in the basal ganglia consistent with their diagnosis.

Detailed physical, neurological, and neuropsychiatric examinations were carried out as follows: the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) to assess cognitive status, the Geriatric Depression Scale (GDS) to assess depressive symptoms (Sheikh and Yesavage, 1986), the Neuropsychiatric Inventory (NPI) to assess neuropsychiatric symptoms (Cummings et al., 1994), the Clinical Assessment of Fluctuation Scale (CAFS) to assess fluctuating cognition (Walker et al., 2000), and the motor subsection of the Unified Parkinson's Disease Rating Scale (UPDRS III) for motor features of parkinsonism (Fahn and Elton (1987)). Exclusion criteria were severe concurrent illness (apart from dementia in the DLB and AD groups), the presence of space-occupying lesions on MRI, stroke history and any contraindications to MRI. None of the control subjects had a history of psychiatric illness. A larger control group size was used to obtain a robust depiction of the brain networks in the older brain.

2.2. Imaging

All subjects were scanned on the same 3 T MRI system (Intera Achieva scanner, Philips Medical System, Eindhoven, The Netherlands). An eight-channel head coil was used to collect resting state fMRI scans using a gradient-echo echo-planar imaging sequence. The scan timings and parameters were as follows: 25 axial slices, 128 volumes, anterior–posterior acquisition, in-plane resolution $=2\times2$ mm^2, slice thickness $=6$ mm, repetition time $=3000$ ms, echo time $=40$ ms, field of view $=260\times150\times260$ mm^3, acquisition time $=6.65$ min. Conventional structural 3D T1-weighted scans were also collected and used for co-registration of the functional scans.

2.3. Resting state fMRI analysis

2.3.1. Data pre-processing

Data were analysed using the FMRIB's Software Library (FSL) tools (version 4.1.9) (www.fmrib.ox.ac.uk/fsl) (Smith et al., 2004). Pre-processing using FMRI Expert Analysis Tool (FEAT) (version 5.98) involved head-motion correction (Jenkinson et al., 2002), removal of non-brain tissue (Smith, 2002), spatial smoothing (Gaussian 6-mm full width at half-maximum), high-pass temporal filtering (120 s), affine-registration to the subjects' anatomical T1-weighted scan and subsequently to the Montreal Neurological Institute (MNI) 152 standard space template (Jenkinson and Smith, 2001).

2.3.2. Independent component analysis

First, resting state networks in every study subject were identified using a model-free independent component analysis (ICA) approach, multivariate exploratory linear optimised decomposition into independent components (MELODIC) (Beckmann et al., 2005; Beckmann and Smith, 2004, 2005). Spatiotemporal components for each subject were examined, and components that clearly corresponded to noise (e.g., scanner-related or physiological artefacts) were removed (FSL software tool fslregfilt) based on their spatial patterns and temporal frequency characteristics (Beckmann and Smith, 2005), similar to previous studies (de Bie et al., 2012). The filtered and noise-free data were then used for the group analysis. This involved combining all subjects' ($n=68$) resting state scans into a single 4D data set, which was then decomposed into spatio-temporal components (multi-session temporal concatenation approach) (Beckmann et al., 2005). These component maps were divided by the standard deviation of the residual noise and thresholded at a posterior probability threshold of $p>0.5$ (i.e., an equal loss is placed on false positives and false negatives) by fitting a Gaussian/gamma mixture model to the histogram of intensity values (Beckmann and Smith, 2004). The number of components was restricted to 25, which has previously been shown to be the optimal number to split fMRI datasets into a final set of spatially independent components (Damoiseaux et al., 2006, 2012). These independent components were inspected visually, and specific networks were identified for further analysis, following spatial correlation against resting state networks previously reported (Beckmann et al., 2005; Smith and Nichols, 2009), i.e., default mode, salience, executive control, basal ganglia and limbic networks (see Fig. 1), as they were expected to be affected in DLB based on the symptom profile.

2.3.3. Dual regression approach

For the networks shown in Fig. 1 (identified from the group ICA analysis), functional connectivity differences among DLB, AD and control subjects were investigated on a voxel-wise basis using a dual regression approach (Filippini et al., 2009; Veer et al., 2010), carried out separately for each independent component, similar to previous reports (Cole et al., 2010; Filippini et al., 2012). This involved the following:

i. *Representations of the networks identified in all subjects were created in every individual subject:* First regression to extract individual time series associated with each subject and the component of interest followed by a second regression to obtain subject specific maps that were then transformed into *z*-scores.
ii. *Assessment of statistical differences between DLB, AD and controls:* FSL Randomise (version 2.1) and threshold-free cluster enhancement (TFCE) (Smith and Nichols, 2009) were used to derive separate null distributions of *t*-values for the contrasts reflecting the between- and within-group effects by performing 5000 random permutations and testing the difference between groups or against zero for each iteration (Nichols and Holmes, 2002). Thus, a three-group comparison was carried out to investigate connectivity differences between DLB, AD and controls for each network and the resulting statistical maps thresholded at $p<0.05$ (only family-wise error [FWE] corrected *p*-values <0.05 were accepted and thus the chance of one more false positives occurring over space is no more than 5% and so a 95% confidence of no false positives in the image). Group comparisons were masked using the network identified from all study subjects (see Supplementary material Fig. 1) so that only differences within the network of interest were investigated (Veer et al., 2010). Brain