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Research report

Divergent functional connectivity during attentional processing in Lewy body dementia and Alzheimer's disease

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ABSTRACT

Attention and executive dysfunction are features of Lewy body dementia (LBD) but their neuroanatomical basis is poorly understood. To investigate underlying dysfunctional attention-executive network (EXEC) interactions, we examined functional connectivity (FC) in 30 patients with LBD, 20 patients with Alzheimer's disease (AD), and 21 healthy controls during an event-related functional magnetic resonance imaging (fMRI) experiment. Participants performed a modified Attention Network Test (ANT), where they were instructed to press a button in response to the majority direction of arrows, which were either all pointing in the same direction or with one pointing in the opposite direction. Network activations during both target conditions and a baseline condition (no target) were derived by (ICA) Independent Component Analysis, and interactions between these networks were examined using the beta series correlations approach.

Our study revealed that FC of ventral and dorsal attention networks DAN was reduced in LBD during all conditions, although most prominently during incongruent trials. These alterations in connectivity might be driven by a failure of engagement of ventral attention networks, and consequent over-reliance on the DAN. In contrast, when comparing AD patients with the other groups, we found hyperconnectivity between the posterior part of the default mode network (DMN) and the DAN in all conditions, particularly during incongruent trials. This might be attributable to either a compensatory effect to overcome

Abbreviations: AD, Alzheimer's disease; ANT, Attention network test; CAF, Clinical assessment of fluctuations; CAMCOG, Cambridge Cognitive Examination; DAN, Dorsal attention network; DMN, Default mode network; EXEC, Executive network; FC, Functional connectivity; LBD, Lewy body dementia; ICA, Independent component analysis; MPFC, Medial prefrontal cortex; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; PCC, Posterior cingulate cortex; ROI, Region of interest; UPDRS, Unified Parkinson's disease rating scale; VAN, Ventral attention network.

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DMN dysfunction, or be arising as a result of a disturbed transition of the DMN from rest to task.

Our results demonstrate that dementia syndromes can be characterized both by hyper- and hypoconnectivity of distinct brain networks, depending on the interplay between task demand and available cognitive resources. However these are dependent upon the underlying pathology, which needs to be taken into account when developing specific cognitive therapies for LBD as compared to Alzheimer's.

1. Introduction

Lewy body dementia (LBD), which includes both dementia with Lewy bodies and Parkinson's disease dementia, is the second most common cause of neurodegenerative dementia after Alzheimer's disease (AD) (Vann Jones & O'Brien, 2014). In addition to visual hallucinations and parkinsonism, patients frequently experience fluctuating cognition, particularly in the domains of attention and executive function. However the patho-biological underpinnings of these key cognitive symptoms are poorly understood.

It has been long established that neurodegenerative diseases do not simply represent a combination of dysfunctions or lesions of discrete brain areas, but can also be viewed as disconnection syndromes (Morrison et al., 1986). There is a considerable body of evidence showing impaired communication of various brain regions during functional magnetic resonance imaging (fMRI) of blood oxygen level dependent (BOLD) resting state in LBD and AD, particularly affecting attention and executive networks (EXEC) (Franciotti et al., 2013; Peraza et al., 2014; Wang et al., 2006). Another apposite network is the default mode network (DMN) which is active during rest and deactivates during tasks (Binder, 2012; Buckner, Andrews-Hanna, & Schacter, 2008; Greicius, Krasnow, Reiss, & Menon, 2003; Shulman et al., 1997), allowing the transfer of neural resources from internal processing to other networks such as attentional networks (Kelly, Uddin, Biswal, Castellanos, & Milham, 2008). In AD, previous studies have reported decreased activity in the DMN during the resting state (Agosta et al., 2012; Dipasquale et al., 2015; Rombouts, Barkhof, Goekoop, Stam, & Scheltens, 2005) whereas in LBD, resting state studies have shown conflicting results, ranging from no change in DMN activity at rest compared to aged controls (Franciotti et al., 2013; Peraza et al., 2014) through to reduced activity (Lowther, O'Brien, Firbank, & Blamire, 2014).

Whilst there are common connectivity patterns during tasks and at rest (Beckmann, DeLuca, Devlin, & Smith, 2005; Fox, Corbetta, Snyder, Vincent, & Raichle, 2006), the inter-regional correlations are dynamic and depend on task difficulty, task performance and cognitive state (Cole et al., 2013; Krienen, Yeo, Buckner, & Buckner, 2014; McIntosh, Rajah, & Lobaugh, 2003), and thus resting state examinations may only be partially informative. To acquire a fuller understanding of how brain networks are disrupted during attentional and executive dysfunction in LBD, interrogation of brain activity during a task may provide a more complete picture.

In this study of patients with LBD, AD and healthy controls, we analyzed data from a previously reported fMRI dataset (Firbank et al., 2016) acquired by our group where we applied a modified version of the Attention Network Test (ANT), which characterizes dissociable aspects of attention including *alerting*, *orienting* and *conflict* (executive control) (Fan, McCandliss, Sommer, Raz, & Posner, 2002).“ This was performed during fMRI to detect task-related interaction of attentional and EXEC and the DMN. We used independent component analysis (ICA) as a data-driven technique to derive co-activated brain regions throughout the task without the need of an *a priori* hypothesis of a specific network distribution and then compared inter-network connectivity between groups. To explore the relationship between connectivity and attention-executive function, we focussed on the effect of the executive-conflict target stimulus rather than cue elements of the ANT, using beta series correlations; an approach that allows for a separate examination of congruent and incongruent trials (Rissman, Gazzaley, & D'Esposito, 2004).

We hypothesized that we would see a dysfunctional coupling of attentional and EXEC with the DMN in LBD and AD. Specifically, we assumed that the interaction of attention networks would be more impaired in LBD, given generally greater attentional impairment in this patient group, whereas in AD we expected that we would find defective coupling of the DMN with other regions, in accordance with previous task based and resting state studies (Damoiseaux, Prater, Miller, & Greicius, 2012; Dipasquale et al., 2015; Rombouts et al., 2005). We also predicted that disturbances in connectivity would increase during task execution compared to baseline and also in relation to the level of task conflict.

2. Methods and participants

2.1. Participants

Patients aged over 60 years with mild to moderate dementia (Mini-Mental State Examination – MMSE > 12) were recruited from local old age psychiatry and neurology services. Two experienced senior clinicians applied the revised International Consensus Guidelines for dementia with Lewy bodies (McKeith et al., 2005), Emre criteria for Parkinson's disease with dementia (Emre et al., 2007) and National Institute on Aging (NIA) criteria for AD (McKhann et al., 2011) to independently diagnose probable AD, dementia with Lewy bodies or Parkinson's disease dementia. As our previous imaging