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# Neurophysiological biomarkers for Lewy body dementias

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HIGHLIGHTS

- Biomarkers are needed to improve Lewy body dementia (LBD) diagnosis and measure treatment response.
- There is substantial heterogeneity in neurophysiology biomarker methodologies limiting comparison.
- However, there is tentative evidence to suggest neurophysiological approaches may show promise as potential biomarkers of LBD.

ABSTRACT

*Objective:* Lewy body dementias (LBD) include both dementia with Lewy bodies (DLB) and Parkinson's disease with dementia (PDD), and the differentiation of LBD from other neurodegenerative dementias can be difficult. Currently, there are few biomarkers which might assist early diagnosis, map onto LBD symptom severity, and provide metrics of treatment response. Traditionally, biomarkers in LBD have focussed on neuroimaging modalities; however, as biomarkers need to be simple, inexpensive and non-invasive, neurophysiological approaches might also be useful as LBD biomarkers.
*Methods:* In this review, we searched PubMED and PsycINFO databases in a semi-systematic manner in order to identify potential neurophysiological biomarkers in the LBDs.
*Results:* We identified 1491 studies; of these, 37 studies specifically examined neurophysiological biomarkers in LBD patients. We found that there was substantial heterogeneity with respect to methodologies and patient cohorts.
*Conclusion:* Generally, many of the findings have yet to be replicated, although preliminary findings reinforce the potential utility of approaches such as quantitative electroencephalography and motor cortical stimulation paradigms.
*Significance:* Various neurophysiological techniques have the potential to be useful biomarkers in the LBDs. We recommend that future studies focus on maximising the diagnostic specificity and sensitivity of the most promising neurophysiological biomarkers.


## 1. Introduction

Dementia with Lewy bodies (DLB) is the second most common cause of degenerative dementia in older people after Alzheimer's disease (AD), where approximately 10–15% of dementia cases demonstrate Lewy body pathology at autopsy (McKeith, 2006). In Parkinson's disease (PD), dementia is a common outcome and up to 80% of PD patients eventually develop dementia as the disease progresses (Aarsland et al., 2003; Hely et al., 2008). Collectively, DLB and Parkinson's disease dementia (PDD) can be grouped under the umbrella term of Lewy body dementias (LBD) due to the overlap in symptom profile, similar treatment response, and common underlying neuropathology of alpha-synuclein aggregation (Francis, 2009). Individuals with LBD therefore represent an

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important disease group in older age, with a significant corresponding impact upon health and society.

Cognitively, LBD patients display marked deficits in executive and visuo-spatial/visuo-perceptual function, and variations in their levels of arousal and attention; the latter are typically referred to as 'cognitive fluctuations' (Lee et al., 2012; McKeith et al., 2005; Mollenhauer et al., 2010; Mosimann et al., 2004). Additional clinical features include spontaneous Parkinsonism motor features (McKeith et al., 2005), but non-motor manifestations such as visual hallucinations, autonomic dysfunction, syncope, repeated falls, rapid eye movement sleep behaviour disorder (RBD), delusions and depression are also typical in the LBDs and can cause significant difficulties for patients (McKeith et al., 2005).

There are a number of treatment challenges in the LBDs. Profound cholinergic deficits occur in LBD, and are even more apparent than those observed in AD (Samuel et al., 2000). The remediation of cholinergic function, by the use of cholinesterase inhibitors such as donepezil, rivastigmine and galantamine, may have cognitive and neuropsychiatric benefits, including improvements in global cognitive function, attentional function and activities of daily living (McKeith et al., 2004). However, intra-individual variations are frequently observed in the response to these treatments (Burn and McKeith, 2003) and responder stratification, through the use of apposite biomarkers, would aid the clinical management of LBD. Beyond the cholinesterase inhibitors, there are few efficacious pharmacological treatment options, and agents such as memantine have been tried with mixed success (Aarsland et al., 2009; Emre et al., 2010; Matsunaga et al., 2015). Consequently, there is now a great deal of interest in the search for viable and specific biomarkers in LBD, as these would assist the development of novel therapeutics and provide an accurate method for monitoring treatment response.

Existing candidate biomarkers, which have been used in the LBDs, have included clinical, biochemical, genetic, and neuroimaging markers, such as alpha-synuclein or amyloid beta levels within cerebrospinal fluid (CSF), or alpha-synuclein gene mutations (Hanagasi et al., 2013; Lippa et al., 2007). Generally, the utility of these candidate biomarkers has only been supported in a research context, aside from dopamine transporter imaging, which due to its high specificity in differentiating DLB from AD (McKeith et al., 2007) is now recommended clinically as a method for confirming the diagnosis of DLB in uncertain cases (Mak et al., 2014). However, dopamine transport imaging remains expensive, exposes an individual to radioactivity and provides little or no information regarding the disease progression or prognosis. Additionally, this method does not overtly correlate with the severity of cognitive or neuropsychiatric symptoms in DLB. Similarly whilst magnetic resonance imaging (MRI) has been shown to be a useful tool in the differential diagnosis of the dementias (Mak et al., 2014) its use in LBD is relatively limited and compared to other imaging modalities, MRI has the disadvantage of being relatively high in cost. Alternatively, cerebrospinal fluid (CSF) examination has also been mooted as a potential biomarker in LBD, where one potential application might include the assessment of alpha-synuclein levels (Mukaetova-Ladinska et al., 2010). However, the clinical utility of this approach remains uncertain, and further methodological developments are required prior to routine use (Lim et al., 2013). A further disadvantage of the use of CSF as a biomarker is that it cannot be collected in a non-invasive manner.

In summary, there is a clear and pressing need to identify useful biomarkers of LBD in order to: (1) expedite the early diagnosis of LBD and enable differential diagnosis to be obtained, particularly during the prodromal phase of the disease; (2) improve our understanding of LBD progression; (3) provide a means to accurately monitor the therapeutic response to treatment; and (4) ultimately develop early disease-modifying interventions. One modality which has not been extensively examined in LBD is the use of neurophysiological approaches, despite their increasing relevance in AD (de Waal et al., 2011; van Straaten et al., 2014). As biomarkers should ideally be non-invasive, inexpensive, simple to use and technically validated (Gerlach et al., 2012), in this regard, a variety of neurophysiological techniques, and in particular electroencephalography (EEG), may be useful biomarkers of LBD.

In the present review we therefore sought to explore the relevant literature in order to identify the way in which neurophysiological approaches have been applied in LBD. Specifically, we sought to evaluate their diagnostic utility, assess whether these markers map onto symptomatic phenotypes, and finally, examine their performance as potential markers of treatment response.

## 2. Method

### 2.1. Search methods and inclusion/exclusion criteria

In order to identify the available literature regarding current and potential neurophysiological biomarkers in LBD, PubMED (until 29 April 2015) and PsycINFO (from 1967 until April Week 3 2015) databases were searched independently by two of the authors (RAC & GJE) using the following terms: "Lewy*", "Parkinson's disease with dementia", "Parkinson's disease with mild cognitive impairment", "dementia with Lewy*" AND "bereit schaftspotential", "biomarker", "blink recovery", "blink reflex", "contingent negative variation", "cortical silent periods", "EEG", "electroencephalography", "electrophysiology", "ERP", "event-related potential", "evoked potential", "flicker fusion", "flutter fusion" "H-reflex", "induced potential", "intra-cortical facilitation", "ipsilateral silent periods", "LDAEP", "long-interval intracortical inhibition", "long-latency stretch reflex", "magnetoencephalography", "MEG", "mismatch negativity", "motor evoked potential", "nerve stimulation", "neurophysiology", "prepulse inhibition", "SAI", "short afferent inhibition", "short-interval intracortical inhibition", "startle", "sympathetic skin response", "TMS" and "transcranial magnetic stimulation".

Studies which focussed only on the clinical phenotype of LBD, those which focussed on the behavioural aspects of LBD, or studies which employed exclusively neuroimaging techniques, were excluded. This search strategy (Fig. 1) resulted in a total of 1491 potential articles. Article titles and abstracts were screened for relevance, and the reference sections of included papers were searched in order to identify any additional studies. Review, non-English and duplicate articles were removed.

For an article to be included, LBD participants were required to have met established diagnostic criteria for either probable DLB or PDD (Emre et al., 2007; McKeith et al., 2005), or, for PDD studies published prior to the 2007 criteria, on the basis of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 1994), or LBD participants who had neuropathological post-mortem confirmation of their diagnosis, in accordance with previously-published guidelines (Fujishiro et al., 2008; McKeith et al., 2005). This resulted in a final total of 37 studies.

## 3. Results

The most common modality used was EEG, as a total of 24 EEG studies were identified (see Supplementary Table S1 for details); 15 of which predominantly examined resting-state EEG and 6 of which examined event-related potentials (ERPs). A total of 12 studies employed a range of other neurophysiological techniques (see Supplementary Table S2) including TMS (5 studies), MEG (2 studies), and the assessment of the blink reflex (2 studies). Studies