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Quantitative electroencephalography as a marker of cognitive fluctuations in dementia with Lewy bodies and an aid to differential diagnosis

Myrto Stylianou [a,*], Nicholas Murphy [a,1], Luis R. Peraza [a], Sara Graziadio [b], Ruth Cromarty [a], Alison Killen [a], John T. O' Brien [c], Alan J. Thomas [a], Fiona E.N. LeBeau [a,2], John-Paul Taylor [a,2]

[a] Institute of Neuroscience, Newcastle University Medical School, Newcastle University, Newcastle upon Tyne, UK
[b] NIHR Newcastle In Vitro Diagnostics Co-operative, Newcastle Upon Tyne Hospitals Foundation Trust, Newcastle upon Tyne, UK
[c] Department of Psychiatry, University of Cambridge, Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK

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HIGHLIGHTS

- EEG slowing was evident in dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) and less in Alzheimer's disease (AD) patients compared to controls.
- Dominant rhythm variability was larger in AD but only correlated with cognitive fluctuations in DLB.
- QEEG variables classified DLB and AD patients with high sensitivity and specificity.

ABSTRACT

Objective: We investigated for quantitative EEG (QEEG) differences between Alzheimer's disease (AD), dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) patients and healthy controls, and for QEEG signatures of cognitive fluctuations (CFs) in DLB.
Methods: We analysed eyes-closed, resting state EEGs from 18 AD, 17 DLB and 17 PDD patients with mild dementia, and 21 age-matched controls. Measures included spectral power, dominant frequency (DF), frequency prevalence (FP), and temporal DF variability (DFV), within defined EEG frequency bands and cortical regions.
Results: DLB and PDD patients showed a leftward shift in the power spectrum and DF. AD patients showed greater DFV compared to the other groups. In DLB patients only, greater DFV and EEG slowing were correlated with CFs, measured by the clinician assessment of fluctuations (CAF) scale. The diagnostic accuracy of the QEEG measures was 94% (90.4–97.9%), with 92.26% (80.4–100%) sensitivity and 83.3% (73.6–93%) specificity.
Conclusion: Although greater DFV was only shown in the AD group, within the DLB group a positive DFV – CF correlation was found. QEEG measures could classify DLB and AD patients with high sensitivity and specificity.
Significance: The findings add to an expanding literature suggesting that EEG is a viable diagnostic and symptom biomarker in dementia, particularly DLB.

1. Introduction

Dementia with Lewy bodies (DLB) is a common type of dementia after Alzheimer's disease, accounting for approximately 10–15% of cases at autopsy (McKeith et al., 2004). DLB is associated with quality of life and significant carer burden. It is frequently underdiagnosed and often misdiagnosed as AD, especially at early stages where both diseases manifest with similar cognitive deficits (Metzler-Baddeley, 2007). Estimates of sensitivity and specificity

* Corresponding author at: Institute of Neuroscience, Newcastle University Medical School, Framlington Place, Newcastle upon Tyne NE2 4HH, UK.
E-mail addresses: M.Stylianou2@ncl.ac.uk (M. Stylianou), Nicholas.Murphy@bcm.edu (N. Murphy), luis.peraza-rodriguez@ncl.ac.uk (L.R. Peraza), sara.graziadio@ncl.ac.uk (S. Graziadio), Ruth.Cromarty@ncl.ac.uk (R. Cromarty), alison.killen@ncl.ac.uk (A. Killen), john.obrien@medschl.cam.ac.uk (J.T. O' Brien), alan.thomas@ncl.ac.uk (A.J. Thomas), fiona.lebeau@ncl.ac.uk (F.E.N. LeBeau), john-paul.taylor@ncl.ac.uk (J.-P. Taylor).
[1] Current address: Baylor College of Medicine, Department of Neuropsychiatry, Houston, TX 77030, USA.
[2] These authors are joint senior authors.

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for DLB diagnosis using established clinical criteria (McKeith et al., 2017) have been quite variable but have a common tendency for relatively high specificity but lower sensitivity (Huang et al., 2013). The fact that DLB patients are sensitive to neuroleptics (McKeith et al., 1992), and demonstrate a faster disease progression compared to other dementias (Ballard et al., 2001), underpin the necessity to improve diagnostic accuracy for this group of patients.

Cognitive fluctuations (CFs) are one of the core symptoms of DLB and refer to spontaneous alterations in cognition, attention and arousal (McKeith et al., 2017). CFs are of clinical importance as they have been correlated with visual hallucinations (Varanese et al., 2010), impairment in daily activities and care burden. Moreover, CFs are an important diagnostic feature for DLB as their prevalence reaches 90% of cases, compared to just 20% of AD and 29% of Parkinson's disease dementia (PDD; Ballard et al., 2002). CFs are also qualitatively different between DLB and AD as in the former case they relate more to executive and perceptual performance, while in the later they are primarily linked to memory impairment (Zupancic et al., 2011). The Clinician Assessment of Fluctuation (CAF) is a clinical scale devised for the psychometric assessment of CFs (Walker et al., 2000). Although CAF is regarded as a fairly reliable measure of CFs if used by an experienced clinician (Van Dyk et al., 2016), the high variability in fluctuation severity and duration of confusional episodes, along with difficulties for informants in separating out what are true intrinsic fluctuations from what are simply responses to external stressors, impose a considerable limitation in CF identification (Bradshaw et al., 2004).

Electroencephalography is an emerging modality for differential diagnosis between dementia subtypes as it is simple, cost-effective, easily accessible and non-invasive compared to imaging approaches. The most prominent QEEG finding in DLB and PDD is a shift of power and dominant frequency (DF) from the alpha frequency range towards high-theta, described as "EEG slowing". This EEG slowing is most prevalent posteriorly (Briel et al., 1999) and although it is also observed in AD patients (Jackson et al., 2008), it is not as prominent as in the Lewy body diseases – DLB and PDD. In studies quantifying differences between DLB or DLB/PDD, or AD and controls, QEEG variables such as coherence (Snaedal et al., 2012), temporal dominant frequency variability (DFV) (Andersson et al., 2008), power ratio between bands and statistical measures such as Granger causality (Garn et al., 2017), have all achieved high diagnostic sensitivity and specificity, reaching 100% in the latter study.

Previous investigations have found electrophysiological correlations of CFs in DLB patients. Early work using quantitative electroencephalography (QEEG) has shown a correlation between epoch-by-epoch DFV and CFs in DLB patients compared with healthy controls (Walker et al., 2000). Later work also showed that DLB patients with CFs had greater DFV compared to AD patients in posterior brain regions, and used the DFV together with other QEEG measures to classify AD, PDD-CFs, PDD-without CFs and DLB patients and controls (Bonanni et al., 2008). More recently, a multi-centre cohort analysis has verified these results (Bonanni et al., 2016).

The aforementioned findings of QEEG signatures in DLB in addition to the fact that the QEEG measures were shown to be correlated with the clinical phenotype of DLB and specifically with CFs, suggest that the QEEG could be utilised to investigate for a neurophysiological divergence between DLB and other dementias. The QEEG investigations performed so far have not yet managed to identify differences (Engedal et al., 2015; Garn et al., 2017) between DLB and PDD. Generally, these Lewy body dementia (LBD) subtypes demonstrate great similarities in neuropathological processes, symptom manifestation and treatment. However, DLB is typically characterised by greater executive dysfunction, more psychiatric symptoms, poorer response to levodopa (L-DOPA) and greater amyloid burden compared to PDD (Edison et al., 2008). Moreover, the onset of motor symptoms precedes that of dementia in PDD while in DLB, dementia appears concurrently or before motor symptoms (McKeith et al., 1992). These discrepancies may indicate differences in the spatio-temporal sequence of pathology, with a predominant brain-stem start and rostral progression in PDD and a cortical inception in DLB (Beyer et al., 2007). Potential QEEG differences between PDD and DLB are of research interest, as they could provide insight for better understanding these LBD subtypes.

Earlier QEEG studies focused on investigating the capacity of such measures in aiding DLB differential diagnosis in clinical settings. Hence, they utilized methods such as assessment by visual observation (Bonanni et al., 2008), or attempted to develop an online method that performs analysis during and right-after EEG acquisition (Garn et al., 2017). Here we took a less clinically-orientated approach, as our primary goal was to characterise and compare the resting EEG rhythm in AD, DLB and PDD patients and in relation to healthy controls, and to investigate for DLB specific signatures of CFs. Thus, we performed extensive pre-processing analysis of the EEG signal and a thorough analysis for differences in QEEG measures within different frequency ranges and brain regions, between diagnostic groups. Based on the literature, we hypothesized that dementia patients will exhibit a differential pattern in the distribution of QEEG measures of power and DF within different frequency ranges compared to healthy controls, and that these QEEG measures in addition to DF variability in time (DFV) will also differ between the dementia groups. We also hypothesized that greater DFV will only characterise LBDs and possibly only DLB, and that greater DFV will correlate with more CFs within these groups. Finally, to assess the possible utility of these measures in the development of biomarkers, the QEEG measures that were found to be significantly different between groups were used to predict dementia diagnosis.

2. Material and methods

2.1. Diagnostic groups

Initially we pre-processed EEG data from 21 healthy controls, 19 AD, 20 DLB and 20 PDD participants (Table 1 for the demographic data of the final groups). Patients were individuals who were referred to local old age psychiatry and neurology services and diagnosis was determined by two independent experienced clinicians (Alan J. Thomas and John-Paul Taylor). Controls were age-matched volunteers. Patients with DLB fulfilled the 2005 and 2017 revised criteria for probable DLB (McKeith et al., 2005, 2017) and patients with PDD fulfilled the criteria for probable PDD (Emre et al., 2007). Individuals with AD met the revised criteria of the National Institute of Neurological and Communicative Diseases and Stroke/AD and Related Disorders Association for probable AD (McKhann et al., 2011). The CAF score was assessed by the clinicians and CFs were defined on the basis that they were typical of those seen in DLB and internally driven rather than a response to external environmental factors. Healthy participants demonstrated no evidence of dementia as determined by the Cambridge Cognitive Examination (CAMCOG) score (>80) and from clinical history. Exclusion criteria for all participants included significant history of neurological or psychiatric conditions. Prescriptions of acetylcholinesterase inhibitors (AChEIs), memantine and dopaminergic medications were allowed. Ethical approval was provided by the Northumberland Tyne and Wear NHS Trust and Newcastle University ethics committee.