




BRIEF REPORT

Slowing on quantitative EEG is associated with transition to dementia in mild cognitive impairment

Calum A. Hamilton,¹  Julia Schumacher,¹  Fiona Matthews,² John-Paul Taylor,¹ Louise Allan,³ Nicola Barnett,¹ Ruth A. Cromarty,¹ Paul C. Donaghy,¹ Rory Durcan,¹  Michael Firbank,¹ Sarah Lawley,¹ John T. O'Brien,⁴ Gemma Roberts,¹ and Alan J. Thomas¹

¹Translational and Clinical Research Institute, Biomedical Research Building, Campus for Ageing and Vitality, Newcastle University, Newcastle upon Tyne, UK

²Population Health Sciences Institute, Biomedical Research Building, Campus for Ageing and Vitality, Newcastle University, Newcastle upon Tyne, UK

³Institute of Health Research, South Cloisters, University of Exeter, St Luke's Campus, Heavitree Road, Exeter, UK

⁴Department of Psychiatry, Herschel Smith Building, University of Cambridge, Cambridge, UK

ABSTRACT

Electroencephalographic (EEG) abnormalities are greater in mild cognitive impairment (MCI) with Lewy bodies (MCI-LB) than in MCI due to Alzheimer's disease (MCI-AD) and may anticipate the onset of dementia. We aimed to assess whether quantitative EEG (qEEG) slowing would predict a higher annual hazard of dementia in MCI across these etiologies. MCI patients ($n = 92$) and healthy comparators ($n = 31$) provided qEEG recording and underwent longitudinal clinical and cognitive follow-up. Associations between qEEG slowing, measured by increased theta/alpha ratio, and clinical progression from MCI to dementia were estimated with a multistate transition model to account for death as a competing risk, while controlling for age, cognitive function, and etiology classified by an expert consensus panel.

Over a mean follow-up of 1.5 years ($SD = 0.5$), 14 cases of incident dementia and 5 deaths were observed. Increased theta/alpha ratio on qEEG was associated with increased annual hazard of dementia (hazard ratio = 1.84, 95% CI: 1.01–3.35). This extends previous findings that MCI-LB features early functional changes, showing that qEEG slowing may anticipate the onset of dementia in prospectively identified MCI.

Key words: quantitative electroencephalography, mild cognitive impairment, dementia with Lewy bodies

Background

Mild cognitive impairment (MCI) develops heterogeneously: this clinical syndrome may be an intermediate stage of cognitive decline between healthy cognitive aging and neurodegenerative dementias, such as Alzheimer's disease (AD) or dementia with Lewy bodies (DLB). However, not all MCI cases progress to dementia, and those that do may differ in their rates of clinical transition.

Identifying specific etiologies in MCI, such as MCI due to AD (MCI-AD) or MCI with Lewy bodies (MCI-LB), may help to prospectively identify cases at risk of dementia, with the latter possibly

having a greater annual risk of clinical transition to dementia (Hamilton *et al.*, 2021). However, there is considerable variability in clinical prognosis within MCI etiologies, not just across them. Specific pathophysiological mechanisms may underlie these associations with progression to dementia, irrespective of etiology; previous research has suggested that abnormalities on electroencephalography (EEG) recordings may be associated with risk-associated clinical features of dementia—visual hallucinations and cognitive fluctuations (Hamilton *et al.*, 2021; Law *et al.*, 2020)—and so may predict dementia onset across etiologies.

Such EEG abnormalities, including qualitative abnormalities and slowing on quantitative EEG (qEEG), have been identified in MCI-AD and MCI-LB as well as their respective dementias, suggesting that these may precede the onset of clinical dementia in some cases. Profiles of abnormalities may

Correspondence should be addressed to: Calum A Hamilton, 3rd Floor Biomedical Research Building, Campus for Ageing and Vitality, Newcastle University, Newcastle upon Tyne, NE4 5PL, UK. Email: Calum.Hamilton@Newcastle.ac.uk Received 22 Apr 2021; revision requested 18 Jun 2021; revised version received 28 Jul 2021; accepted 29 Jul 2021. First published online 23 September 2021

differ between etiologies, often being greater in MCI-LB and DLB (Law *et al.*, 2020), but may also differ within these syndromes: theta/alpha ratio, previously shown to be greater in MCI-LB than MCI-AD and healthy controls (Massa *et al.*, 2020; Schumacher *et al.*, 2020), has been associated with shorter time to dementia in MCI patients who developed DLB (van der Zande *et al.*, 2020). Theta/alpha ratio may therefore be a useful qEEG measure to predict the onset of dementia in prospectively assessed MCI, particularly when Lewy body disease is suspected.

We, therefore, aimed to assess whether slowing of qEEG, measured by increased theta/alpha ratio, would predict the onset of clinical dementia in a prospective MCI cohort, hypothesizing that a greater shift towards slower frequencies would be associated with a greater risk of dementia.

Methods

Participants

PATIENTS

One-hundred and three participants with MCI were included in a longitudinal study, as described previously (Schumacher *et al.*, 2020). These were recruited from older persons healthcare and memory services in North East England. All were aged ≥ 60 years, had a health service diagnosis of MCI, and were considered for eligibility if their medical records reported the possible presence of any core clinical features of DLB (complex visual hallucinations, rapid eye movement sleep behavior disorder [RBD], cognitive fluctuations, or parkinsonism), or any other clinical feature supportive of DLB, but also found in AD (e.g. mood change, sleep disturbance, or autonomic dysfunction). Participants provided written informed consent prior to detailed initial clinical assessment, and were subsequently excluded if this identified the presence of dementia at baseline, absence of objective cognitive impairment, presence of parkinsonism for longer than 12 months prior to the onset of cognitive symptoms, or presence of possible frontotemporal or vascular etiologies. This study received ethical approval from the Newcastle and North Tyneside 2 Research Ethics Committee (15/NE/0420).

COMPARATORS

Thirty-four healthy comparators were recruited from local dementia research participation services, or from friends or families of MCI participants. Inclusion criteria were being age ≥ 60 , and being cognitively healthy with no known brain disease.

All participants in both groups were required to be medically stable at baseline assessment.

Design

All participants underwent detailed assessment at baseline, and longitudinal follow-up (initially at 12-month intervals, but with adaptive scheduling necessitated by COVID-19 from 2020). For healthy comparators, follow-up assessments took place after approximately 12 and 30 months from baseline. For MCI patients, follow-up assessments took place approximately 12, 24, and 42 months from baseline.

Cognitive and clinical assessment

Participants underwent detailed neuropsychological assessment at baseline and follow-up, as described previously (Donaghy *et al.*, 2020). Participants were also assessed in a clinical interview by a study research nurse or medical doctor at baseline and follow-up. This included measures of cognitive function, daily independence, and clinical features of MCI-LB to be assessed by an expert panel of old age psychiatrists (see below).

Imaging

All participants from both MCI and cognitively healthy groups were offered ^{123}I -Nfluoropropyl-2 β -carbomethoxy-3 β -(4-iodophenyl) single photon emission computed tomography (FP-CIT SPECT) and ^{123}I iodine-metaiodobenzylguanidine (MIBG) at baseline, with FP-CIT also repeated at first follow-up. FP-CIT imaging in this cohort has been described previously in detail (Roberts *et al.*, 2020); briefly, images were visually rated as normal or abnormal by a panel of trained image analysts, blind to diagnostic information. Delayed MIBG images were separately quantified as described previously (Roberts *et al.*, 2021), blind to diagnosis, using a heart:mediastinum ratio abnormality cutoff of <1.86 . Results for each imaging modality were then incorporated into differential classifications of MCI.

Diagnosis

At baseline and after each follow-up, a three-person panel of experienced old age psychiatrists independently reviewed research notes from the clinical interview, and rated (A) the presence or absence of MCI according to National Institute on Aging at National Institutes of Health and the Alzheimer's Association criteria (Albert *et al.*, 2011), or all-cause dementia and (B) the presence or absence of each of the four core clinical features of MCI-LB (complex visual hallucinations, RBD, cognitive fluctuations, and parkinsonism).

Table 1. Baseline characteristics of cohort with qEEG available

| | MCI | | | |
|-------------------------------------|---------------------|----------------|-------------------------|-------------------------|
| | CONTROL (N = 31) | AD (N = 36) | POSSIBLE LB (N = 17) | PROBABLE LB (N = 39) |
| Female gender | 9 (29.0%) | 21 (58.3%) | 7 (41.2%) | 4 (10.3%) |
| Age | 73.7 (7.3) | 76.1 (7.7) | 74.1 (7.3) | 74.7 (6.4) |
| ACE-R Mini-Mental State Examination | 28.5 (1.1) | 26.9 (2.1) | 25.9 (3.0) | 26.6 (2.5) |
| ACE-R total | 92.7 (4.2) | 82.4 (8.5) | 77.5 (11.6) | 83.8 (9.2) |
| Follow-up years | 1.09 [0.12, 2.32] | 1.00 [0, 3.61] | 1.03 [0, 3.63] | 1.99 [0, 3.67] |
| Years in education | 15 [8.5, 24] | 11 [10, 20] | 11 [9, 25] | 11 [9, 21] |
| Receiving cholinesterase Inhibitors | 0 (0%) | 7 (19.4%) | 3 (17.6%) | 18 (46.2%) |
| Theta/alpha ratio | 0.336 (0.173) | 0.416 (0.164) | 0.464 (0.189) | 0.506 (0.210) |

Mean (SD), median [range], or count (%).

Including these ratings, FP-CIT and MIBG imaging, MCI diagnoses were characterized as either MCI-AD (Albert *et al.*, 2011), or MCI-LB according to current research diagnostic criteria (McKeith *et al.*, 2020): probable MCI-LB given the presence of 2+ core clinical features of DLB in MCI, or one core feature and abnormal FP-CIT or MIBG imaging; possible MCI-LB given the presence of 1 core feature of DLB, or 0 core features with abnormal FP-CIT or MIBG; MCI-AD given normal FP-CIT, MIBG, and 0 core features of DLB. These diagnoses were updated after follow-up if there was new clinical information to change previous ratings, emergent clinical features of DLB, or change in the repeat FP-CIT.

A diagnosis of dementia was made when the participant was judged by the panel to no longer function independently, thus not meeting the criteria for MCI. After diagnosis of dementia, participants were withdrawn from further follow-up.

EEG recording and processing

As described previously (Schumacher *et al.*, 2020), all included participants were offered EEG recording at baseline. Resting state eyes-closed EEG was recorded from 128 electrodes using Waveguard caps (ANT Neuro). Preprocessing was performed using the EEGLAB toolbox in Matlab (R2017a) and included the following steps: bandpass filtering between 0.3 and 54 Hz, segmentation of the EEG into 2-s long nonoverlapping epochs, visual inspection and exclusion of noisy channels and epochs, and independent component analysis for identifying and removing artifacts representing muscular, cardiac, ocular, or electrical line noise. Excluded channels were then replaced using spherical spline interpolation, and the data were average-referenced. From each participant's EEG, the first 45 artifact-free epochs were selected for further analysis, out of

a maximum of 150 epochs. This ensured as many participants could be included as possible, while excluding artifacts related to drowsiness and movements which are more likely further into the recording.

Power spectral density was estimated for each 2-s epoch using Bartlett's method in Matlab with a frequency resolution of 0.5 Hz and a Hamming window. Mean band power within the theta (4–5.5 Hz) and alpha (8–13 Hz) frequency bands was calculated as described previously (Schumacher *et al.*, 2020), and the average theta/alpha ratio across all electrodes was computed.

Longitudinal analysis

A competing risks model was estimated with the *msm* package for R to assess the associations between qEEG slowing, as measured by theta/alpha ratio, and risks of clinical transition from MCI to dementia. This model accounted for death as a competing outcome, with exactly observed transition times, and controlled for additional hazards with a theorized association with a faster decline to dementia including chronological age (centered at 74 years) and baseline global cognitive performance (Addenbrooke's Cognitive Examination – Revised [ACE-R] Total Score). All MCI subgroups were included under a single MCI state, with etiology included as a covariate due to previously observed associations between the MCI-LB syndrome and risk of dementia onset (Hamilton *et al.*, 2021). Theta/alpha ratios and ACE-R scores were standardized into Z-scores from the healthy group data, and comparators were not included in the analysis of dementia conversion.

Gender and education, which were not found to significantly predict dementia transitions in a larger cohort (Hamilton *et al.*, 2021), were not included as covariates.

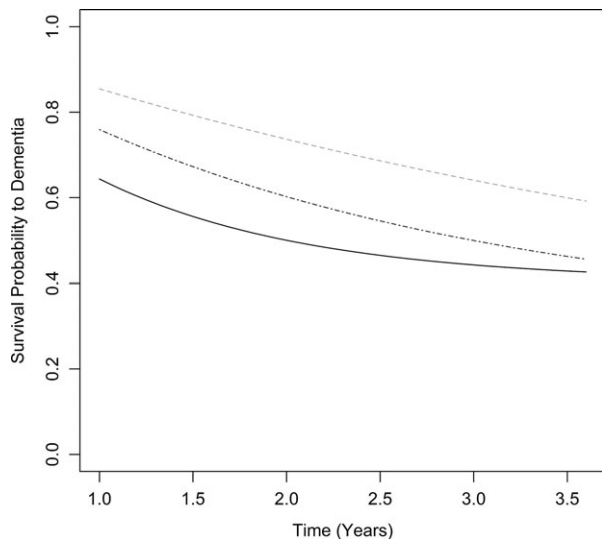


Figure 1. Estimated dementia-free survival in MCI with greater EEG slowing from healthy norm (lighter gray, dashed), +1 SD (darker gray, dash and dot), and +2 SD (black, solid) theta/alpha ratio.

Data availability

Data supporting these analyses are available upon reasonable request through the Medical Research Council Dementias Platform UK (study: ‘SUPeRB’).

Results

Demographics and baseline

One-hundred and twenty-three participants had qEEG available (Table 1); data were not available for 3 comparators and 11 MCI.

Longitudinal analysis

Fourteen cases of dementia were observed following baseline diagnosis of MCI (mean = 1.5 years after baseline, SD = 0.5), and five deaths (mean = 1.9 years after baseline, SD = 1.3). Of five cases of dementia due to AD, all five had previous diagnoses of MCI-AD; there were nine cases of probable DLB, all nine had earlier diagnoses of probable MCI-LB.

The estimated transition rates from MCI to dementia given a healthy mean theta/alpha ratio (Z-score of 0) were 14.5% over 1 year, 26.3% over 2 years, and 35.9% over 3 years (controlling for age, cognition, and MCI subtype). However, this hazard significantly increased with increasingly slower qEEG profiles [hazard ratio (HR) = 1.84, 95% CI: 1.01–3.35 per 1 SD increase in theta/alpha ratio, $Z = 1.99$, $p = .046$; see Figure 1]. For a 1 SD increase in theta/alpha ratio, this corresponded to estimated MCI to dementia transition rates of 24.1% over 1 year, 40.0% over 2 years, and 50.0% over 3 years.

In a sensitivity analysis controlling for the presence of complex visual hallucinations and cognitive fluctuations, previously found to be associated with worse prognosis in MCI in a larger cohort including this sample, this effect was no longer evident (HR = 1.17, 95% CI: 0.66–2.07). However, there was no clear association between theta/alpha ratio in MCI-LB and severity of either visual hallucinations as rated by the North-East Visual Hallucinations Inventory ($\rho = -0.1$, $p = .607$) or cognitive fluctuations as rated by the Dementia Cognitive Fluctuation Scale ($\rho = 0.1$, $p = .517$).

In a further analysis instead controlling for use of cholinesterase inhibitors in MCI, again this effect was no longer evident (HR = 1.80, 95% CI: 0.97–3.32). MCI-LB were more likely to be in receipt of cholinesterase inhibitors than MCI-AD, but within diagnostic groups, there were no significant differences found with a Mann–Whitney U test in theta/alpha ratio between those receiving and those not receiving cholinesterase inhibitors (MCI-AD: $W = 61$, $p = .163$; MCI-LB: $W = 277$, $p = .223$).

Discussion

We hypothesized that greater qEEG slowing would predict transition to dementia; our finding that an increased theta/alpha ratio was associated with an increased hazard of dementia per year supported this. These findings are consistent with previous observations of a shorter time to DLB from MCI with a greater theta/alpha ratio (van der Zande *et al.*, 2020), and suggest that regardless of etiological classification, qEEG slowing may anticipate the onset of dementia in prospectively identified MCI; a clinically complex group with uncertain prognosis.

There may be a mediating role of the pathophysiological mechanisms underlying EEG abnormalities in the relationship between neurodegenerative etiology, clinical features, and longitudinal prognosis. Previous research has suggested that such EEG abnormalities in MCI may reflect loss of cholinergic drive associated with nucleus basalis of Meynert degeneration; greater cholinergic dysfunction in MCI-AD or MCI-LB may therefore be associated with faster progression to dementia, along with qEEG slowing, cognitive decline, and clinical features of DLB such as fluctuating cognition and visual hallucinations (Law *et al.*, 2020).

Limitations

While dementia onset was typically soon after EEG recording, and overall follow-up was brief, all participants had clinically judged MCI at the time of

recording, and differences in baseline cognitive function were controlled for in the state transition analysis. While the estimated annual dementia incidence in this cohort is consistent with past research on prospectively identified MCI, the absolute number of dementia cases was low.

This provides early, marginal evidence that electrophysiological biomarkers may anticipate onset of dementia in MCI across LB and AD etiologies in prospective settings. This extends previous findings from functional magnetic resonance imaging studies (Schumacher *et al.*, 2021) to suggest that early-identified functional abnormalities may anticipate clinical progression in neurodegenerative disease.

Conflicts of interest

None.

Authors' roles

C. Hamilton undertook data collection, analysis of longitudinal data, and drafted the manuscript.

J. Schumacher processed and analyzed qEEG data, and co-wrote the manuscript.

F. Matthews supervised data analysis and reviewed the manuscript's intellectual content.

J.P. Taylor co-designed the study, contributed to the diagnostic panel, and reviewed the manuscript's intellectual content.

L. Allan co-designed the study and reviewed the manuscript's intellectual content.

N. Barnett contributed to data collection and reviewed the manuscript's intellectual content.

R. Cromarty contributed to data collection and reviewed the manuscript's intellectual content.

P. Donaghy co-designed the study, contributed to the diagnostic panel, and reviewed the manuscript's intellectual content.

R. Durcan contributed to data collection and reviewed the manuscript's intellectual content.

M. Firbank contributed to data collection and reviewed the manuscript's intellectual content.

S. Lawley contributed to data collection and reviewed the manuscript's intellectual content.

J. O'Brien co-designed the study and reviewed the manuscript's intellectual content.

G. Roberts contributed to data collection and reviewed the manuscript's intellectual content.

A. Thomas co-designed the study, supervised data collection, contributed to the diagnostic panel, and reviewed the manuscript's intellectual content.

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