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

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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 onset of dementia. We aimed to assess whether quantitative EEG (qEEG) slowing would predict a higher annual hazard of dementia in MCI across these aetiologies.

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 multi-state transition model to account for death as a competing risk, while controlling for age, cognitive function, and aetiology classified by an expert consensus panel.

Over a mean follow up of 1.5 years (SD = 0.5) fourteen cases of incident dementia and five 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 onset of dementia in prospectively-identified MCI.

Background

Mild cognitive impairment (MCI) develops heterogeneously: this clinical syndrome may be an intermediate stage of cognitive decline between healthy cognitive ageing 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 aetiologies 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 aetiologies, not just across them. Specific pathophysiological mechanisms may underlie these associations with progression to dementia, irrespective of aetiology; 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 aetiologies.

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 onset of clinical dementia in some cases. Profiles of abnormalities may differ between aetiologies, 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 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 onset of clinical dementia in a prospective MCI cohort, hypothesising that a greater shift towards slower frequencies would be associated with greater risk of dementia.

Methods

Participants

Patients

One-hundred and three participants with MCI were included in a longitudinal study, as previously described (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, 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 onset of cognitive symptoms, or presence of possible frontotemporal or vascular aetiologies. 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 previously described (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-2β-carbomethoxy-3β-(4-iodophenyl) single photon emission computed tomography (FP-CIT SPECT) and ^{123}iodine-metaiodobenzylguanidine (MIBG) at baseline, with FP-CIT also repeated at first follow-up. FP-CIT imaging in this cohort has been previously described 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 previously described (Roberts *et al.*, 2021), blind to diagnosis, using a heart:mediastinum ratio abnormality cut-off 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 NIA-AA 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, REM sleep behaviour disorder, cognitive fluctuations, and parkinsonism).

Including these ratings, FP-CIT, and MIBG imaging, MCI diagnoses were characterised 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 criteria for MCI. After diagnosis of dementia, participants were withdrawn from further follow-up.

EEG Recording and Processing

As previously described (Schumacher *et al.*, 2020), all included participants were offered EEG recording at baseline. Resting state eyes-closed EEG were 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 non-overlapping epochs, visual inspection and exclusion of noisy channels and epochs, and independent component analysis for identifying and removing artefacts 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 artefact-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 artefacts 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 bandpower within the theta (4-5.5 Hz) and alpha (8-13 Hz) frequency bands was calculated as previously described (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 theorised association with faster decline to dementia including chronological age (centred at 74 years) and baseline global cognitive performance (Addenbrooke's Cognitive Examination – Revised (ACE-R) Total Score). All MCI sub-groups were included under a single MCI state, with aetiology 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 standardised into Z-scores from the healthy group data, and comparators were not included in 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.

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; 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 previous 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 hypothesised 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 aetiological 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 aetiology, clinical features, and longitudinal prognosis. Previous research has suggested that such EEG abnormalities in MCI may reflect loss of cholinergic drive associated with NBM 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 aetiologies in prospective settings. This extends

previous findings from fMRI studies (Schumacher *et al.*, 2021) to suggest that early-identified functional abnormalities may anticipate clinical progression in neurodegenerative disease.

Conflicts of Interest Statement

None

Author Roles

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

J. Schumacher processed and analysed 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

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

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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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Table and Figure Headings

Table 1. Baseline characteristics of cohort with qEEG available.

		MCI		
	Control (N=31)	**AD (N=36)**	**Poss. LB (N=17)**	**Prob. 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)
MMSE	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 (%).

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