Word Count: 3619

Cognitive decline in mild cognitive impairment with Lewy bodies or Alzheimer's disease: a prospective cohort study

Calum A Hamilton MSc[1]*, Fiona E Matthews PhD[2], Paul C Donaghy PhD[1], John-Paul Taylor PhD[1], John T O'Brien DM[3], Nicola Barnett MSc[1], Kirsty Olsen MSc[1], Jim Lloyd PhD[4], George Petrides MBBS[4], Ian G McKeith MD[1], Alan J Thomas PhD[1]

*Corresponding author: Calum A. Hamilton, E-mail: C.Hamilton3@newcastle.ac.uk, Telephone: +447969007442
Postal Address: 3rd Floor Biomedical Research Building, Campus for Ageing and Vitality, Newcastle University, Newcastle upon Tyne, NE4 5PL.

1 Translational and Clinical Research Institute, Biomedical Research Building, Newcastle University, Newcastle upon Tyne, NE4 5PL, United Kingdom
2 Population Health Sciences Institute, Baddiley-Clark Building, Newcastle University, Newcastle upon Tyne, NE2 4AX, United Kingdom
3 Department of Psychiatry, Level E4, University of Cambridge School of Clinical Medicine, Cambridge, CB2 0SZ, United Kingdom
4 Nuclear Medicine Department, Royal Victoria Infirmary, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, NE1 4LP, United Kingdom

Funding Organizations. NIHR Newcastle Biomedical Research Centre; Alzheimer's Research UK; GE Healthcare

Keywords: Mild cognitive impairment; dementia with Lewy bodies; longitudinal decline; neuropsychology

ACKNOWLEDGEMENTS

This research was supported by the NIHR Newcastle Biomedical Research Unit (grant numbers BH120812 and BH120878) and by Alzheimer's Research UK (ARUK-PG2015-13). We would like to acknowledge the contributions of the Lewy Body Dementia Association in allowing the use of the Comprehensive Symptom Checklist. The authors also acknowledge the contributions of GE Healthcare who provided the FP-CIT radioligand for this investigator-led study.

CONFLICTS OF INTEREST

John O'Brien has received personal fees from TauRx, Axon, GE Healthcare, Avid / Lilly and Eisai, and grants from Alliance Medical and Avid / Lilly, all outside the submitted work; George Petrides has received personal fees from GE Healthcare, outside the submitted work; Alan Thomas is currently receiving a grant from Alzheimer's Research UK (ARUK-PG2015-13), during the conduct of the study. For the remaining authors none were declared.

ABSTRACT.

Objectives We explored whether the mild cognitive impairment (MCI) stages of dementia with Lewy bodies (DLB) and Alzheimer's disease (AD) differ in their cognitive profiles, and longitudinal progression.

Design A prospective, longitudinal design was utilized with annual follow-up (Max 5 years, Mean 1.9, SD 1.1) after diagnosis. Participants underwent repeated cognitive testing, and review of their clinical diagnosis and symptoms, including evaluation of core features of DLB.

Setting This was an observational study of independently-living individuals, recruited from local healthcare trusts in North East England, UK.

Participants An MCI cohort (n = 76) aged ≥ 60 years was utilized, differentially diagnosed with MCI due to AD (MCI-AD), or possible/probable MCI with Lewy bodies (MCI-LB).

Measurements A comprehensive clinical and neuropsychological testing battery was administered, including ACE-R, trailmaking tests, FAS verbal fluency, and computerized battery of attention and perception tasks.

Results Probable MCI-LB presented with less impaired recognition memory than MCI-AD, greater initial impairments in verbal fluency and perception of line orientation, and thereafter demonstrated an expedited decline in visuo-constructional functions in the ACE-R compared to MCI-AD. No clear diagnostic group differences were found in deterioration speeds for global cognition, language, overall memory, attention or other executive functions.

Conclusions These findings provide further evidence for differences in severity and decline of visuospatial dysfunctions in DLB compared with AD; further exploration is required to clarify

1 when and how differences in attention, executive, and memory functions emerge, as well as
2 speed of decline to dementia.

OBJECTIVE

Lewy body (LB) and Alzheimer's (AD) diseases are the two commonest causes of degenerative dementia (1); the syndromes of dementia with Lewy bodies (DLB) or AD dementia may be distinguished by physical and psychiatric symptoms (2). They also present with different patterns of impairments in particular cognitive domains (3), and have been observed to decline at different rates; various studies report a more aggressive course in DLB than AD in rate of cognitive decline (4), mortality (5) and hospitalization (6). Consequently people with DLB have poorer quality of life (7), and require more health and care resources (8). Evidence of a faster cognitive decline is however mixed, with some studies finding no difference in speed of decline over shorter periods (9).

Dementia in AD typically manifests in episodic memory deficits, (10) likely reflecting degeneration of the medial temporal lobes (MTL) (11), though dysfunctions also occur in other domains (12). DLB has relatively greater impairments in visuospatial, attentional, and executive functions than AD (13, 14), and generally less severe amnestic memory impairments (15) which are related to the degree of MTL atrophy (16).

Mild cognitive impairment (MCI) represents the transitional stage between healthy ageing and dementia (17). MCI in AD (MCI-AD) has a predominantly amnestic cognitive presentation (18, 19) reflecting underlying MTL atrophy (20).

Cross-sectional data have provided preliminary information on the cognitive profiles of MCI with Lewy bodies (MCI-LB) in comparison with MCI-AD and healthy controls (19, 21, 22),

suggesting that the DLB-like cognitive profile of greater visuospatial and executive impairment, and less amnestic memory dysfunction, may already be evident at the MCI stage. There is emerging evidence that the prodromal stages of DLB may differ in their cognitive trajectories from an idiopathic REM sleep behaviour disorder syndrome (23), but the clinical MCI stages of AD and DLB have not been compared longitudinally.

We previously reported the cross-sectional cognitive profiles in an MCI cohort differentially diagnosed as MCI-LB or MCI-AD (21), finding that MCI-LB was associated with poorer performance on the visuospatial component of the Addenbrooke's Cognitive Examination – Revised and a line angle discrimination task, slower mean responses on a digit vigilance test, and fewer responses on one, but not all, tests of verbal fluency. We aimed to utilize the longitudinal data now available to better characterize the cognitive profiles and trajectories of this same cohort.

We hypothesized that MCI-LB and MCI-AD would display differing trajectories of cognitive decline, specifically: greater episodic memory deficits with AD, and greater impairments in visuospatial, attention, and executive functions in DLB. We also hypothesized that MCI-LB would show a more rapid global cognitive decline than MCI-AD, consistent with findings from comparable longitudinal studies of DLB and AD (4).

METHODS

Participants

Recruitment and baseline assessment has been detailed previously (21, 24). Briefly, prospective participants (n = 90) aged 60 or older were recruited from local healthcare trusts, and had a health service clinical diagnosis of MCI defined by concern about and evidence of cognitive decline in one or more domains, with preserved independent functioning and no dementia (17). Additionally, they reported one or more clinical symptoms sensitive, but non-specific, to LB disease (e.g., mood changes, sleep disturbance, or autonomic symptoms), or indication of the presence of any core or supportive DLB features.

Participants with dementia, or Clinical Dementia Rating (CDR) of > 0.5 at baseline were excluded. Based on health service clinical notes and imaging results those with possible significant vascular (25) or frontotemporal (26) etiologies, or parkinsonism pre-dating cognitive impairment by more than one year, were also excluded. Where possible, an informant was sought (spouse, friend, or family member) to provide additional information. Potential participants meeting these criteria proceeded to a consensus clinical panel diagnosis.

Clinical diagnosis

Participants and informants, where available, underwent semi-structured interview and clinical assessment by the equivalent of a board-certified medical doctor (PCD). A three-person consensus clinical panel of experienced Board Certified old age psychiatrists (AJT, PCD, JPT) independently reviewed clinical notes taken from the baseline assessment and confirmed

diagnoses of MCI according to NIA-AA criteria (17). This was based on evidence of minimal functional impairment (thus independent living was maintained) and a CDR of 0 or 0.5, and a history of cognitive decline reported in the clinical research interview by patient and/or informant which had also been identified previously in the health service. To determine the likely etiology of this impairment, the presence or absence of core or suggestive LB symptoms were also rated by the panel, in accordance with the third consensus criteria for DLB (27).

These symptom ratings were made blind to dopaminergic imaging findings; dopaminergic function was assessed with ^{123}I-N-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) single-photon emission computed tomography (FP-CIT SPECT) imaging (28). Images were randomised, coded, and then visually rated as normal/abnormal by an experienced consensus panel blind to clinical information and diagnosis as reported earlier (24); and incorporated into diagnoses. Seventy-four of 76 participants consented to FP-CIT imaging.

Participants received a diagnosis of MCI with probable Alzheimer's disease (MCI-AD) when they had no core or suggestive LB symptoms, a normal FP-CIT scan and an evidence of decline which was characteristic of AD with no evidence for another etiology, i.e., they met the additional NIA-AA criterion (17) of 'etiology of MCI consistent with AD pathophysiologic process' (24); reported cognitive complaints being progressively degenerative, based on clinical notes. As above, those classified as MCI-AD not only had no core features or biomarkers of Lewy body disease but also no features supporting vascular, frontal or other aetiologies. Possible MCI with Lewy bodies (possible MCI-LB) was diagnosed with either one core LB symptom or abnormal FP-CIT scan, and probable MCI with Lewy bodies (probable MCI-LB)

diagnosed with two or more core LB symptoms, or one core symptom and abnormal dopaminergic imaging. Both participants who did not consent to dopaminergic transporter imaging had sufficient clinical LB symptomology for a probable MCI-LB diagnosis without confirmatory biomarkers.

Seventy-seven participants completed baseline assessment and were initially included as previously described (21); one was excluded during follow-up reviews due to diagnosis of a frontotemporal dementia. Final participant count was therefore 76.

Participants were re-assessed every 12 months in a prospective longitudinal design. Symptom presence, and severity of neurocognitive impairment (MCI or dementia) were re-appraised at annual follow-ups by the clinical panel. Participants were not followed-up after transition to dementia.

As the outcome measures of interest, cognitive scores or reported cognitive complaints did not inform differential diagnoses; these were made on the basis of DLB diagnostic features only.

Materials

Cognitive measures

Repeated measures used were the Addenbrooke's Cognitive Examination-Revised (ACE-R), a 100-point cognitive screening test from which Mini-Mental State Examination (MMSE) score was derived, as were domain-specific sub-scores for Attention and Orientation (0-18), Verbal

Fluency (0-14), Memory (0-26), Visuospatial Function (0-16), and Language (0-26). Trail Making Test parts A (TMT-A) and B (TMT-B), and FAS verbal fluency were also administered annually, with the latter two used to assess executive functions.

Computer-run tests included simple (SRT) and binary choice (CRT) reaction, and digit vigilance (DVT) tests of attention, and a line angle discrimination task (LAT) to assess visual perception (29)..

Baseline-only tasks were the Rey Auditory Verbal Learning Test (RAVLT), Graded Naming Test (GNT), and computerized motion-detection task (29). These were not re-administered at follow-up due to time-constraints.

Clinical measures

In the semi-structured interview, the MDS Unified Parkinson's Disease Rating Scale – Motor Examination (UPDRS-III), Epworth Sleepiness Scale (ESS), and Geriatric Depression Scale (GDS) were administered to patients. The Instrumental Activities of Daily Living (IADL) scale, North-East Visual Hallucinations Inventory (NEVHI), Neuropsychiatric Inventory (NPI), Mayo Sleep Questionnaire (MSQ), Clinician Assessment of Fluctuation (CAF), and Dementia Cognitive Fluctuation Scale (DCFS) were administered to informants. CDR and Cumulative Illness Rating Scale for Geriatrics (CIRS-G) were completed on the basis of clinical history.

Analysis

Baseline differences

As reported previously (21), cross-sectional differences between groups were compared at baseline using one-way ANOVA and chi-square tests.

Longitudinal decline

Linear mixed-effects modelling assessed cognitive change in the overall MCI cohort, and any effect of diagnosis. Analyses were undertaken in *R* software using the packages *lme4* (30) and *lmerTest* (31).

Time, as a continuous fixed effect, predicted cognitive outcome, while controlling for conceptually-relevant covariates (education, age, gender). Models included random intercept and slope at the subject level, allowing for correlation between these when indicated by improved model fit as assessed by lowered Akaike Information Criterion (AIC). Diagnostic group was then incorporated as a fixed effect, interacting with time where appropriate, in all models; in the event that diagnosis did not improve model fit, an additional 'best fit' model is also reported to describe cognitive changes in MCI across diagnostic groups.

Development models were fit by full maximum likelihood, and final reported models by restricted maximum likelihood methods. MCI-AD is treated as the reference group for comparison.

Significance level was defined as $p < .05$ and no adjustment was made for multiple testing given the exploratory nature of this analysis, with domain-specific primary hypotheses requiring independent tests.

RESULTS

Diagnostic groups

At the time of data locking, participants had been followed-up for a mean of 1.9 years (*SD* = 1.1, Min = 0, Max = 5).

Thirty-two participants (42%) had transitioned to dementia; seven MCI-AD (30%), five possible MCI-LB (42%), and 20 (49%) probable MCI-LB. Fourteen transitioned within the first year, 12 in the second, five in the third, and one in their fourth. All seven cases of AD dementia had been previously diagnosed with MCI-AD. Of five possible DLB, three had been diagnosed as MCI-AD but subsequently developed LB symptoms, and two had diagnoses of possible MCI-LB. All 20 cases of probable DLB had been diagnosed as probable MCI-LB. In comparison with MCI-AD, a Fisher's exact test did not find diagnosis of possible MCI-LB to be significantly associated with an eventual diagnosis of possible DLB rather than AD (exact $p = .152$). Probable MCI-LB diagnosis was significantly associated with eventual diagnosis of probable DLB versus AD (exact $p < .001$).

Demographics and baseline scores have been reported in detail previously (21) and are summarized in **Table 1**. Diagnostic groups did not differ in age, education, or baseline global cognitive function. Probable MCI-LB presented with greater functional impairment than MCI-AD (lower IADL score), though all subjects had minimal impairments, as reflected by their MCI diagnosis; IADL scores were correlated (Pearson's *r*) with UPDRS-III ($r(66) = -0.30$, $p = .013$) but not ACE-R total scores ($r(66) = 0.07$, $p = .568$) suggesting that these related to motor, not cognitive, impairments. MCI-AD were mostly female, and probable MCI-LB mostly male. Higher daytime sleepiness (ESS), motor impairment (UPDRS-III), and neuropsychiatric symptomology (NPI, GDS-15, NEVHI, CAF, and DCFS) were found in probable MCI-LB; this was expected as these relate to the symptoms used for differential diagnosis (**Table 2**), as was a higher rate of self-reported hyposmia.

Longitudinal change: global cognitive function

To test the hypothesis that LB symptomology would have a faster decline than AD, a model was developed incorporating diagnosis as a fixed effect (**Figure 1**) predicting ACE-R total score; this did not improve model fit. This full model, and alternate best-fitting model, are reported (**Table 3)**. Diagnostic groups did not significantly differ in their initial global cognition, or their decline.

Domain-specific function

This method was repeated for domain-specific measures. Estimates for ACE-R sub-scores are reported in **Table 3**, including diagnosis (full model), interacting with time where appropriate. Best-fit models are also reported in **Table 3** when diagnosis was not observed to have an effect

as indicated by no improvement in model fit. Age, gender, and education were included as covariates in all cases.

Attentional functions (ACE-R Attention & Orientation) significantly declined over time, but there was no effect of diagnosis, with no improvement in model fit.

Overall memory (ACE-R Memory) did not decline over time; incorporating diagnosis did not improve model fit, and diagnoses did not differ in their initial profiles or time-trajectories.

Verbal fluency significantly declined in MCI. In the full model, probable MCI-LB was associated with poorer verbal fluency (ACE-R Fluency) than MCI-AD, with a corresponding improvement in model fit.

Speech and language (ACE-R Language) declined significantly over time. Including diagnosis did not improve fit; there were no differences between groups in initial language impairment or declines thereafter.

For visuospatial functions (ACE-R Visuospatial), including diagnosis as a fixed effect interacting with time provided best fit (**Table 3**). Although probable MCI-LB had a lower baseline visuospatial sub-score, the error term around this was quite large. MCI-AD patients did not significantly decline in visuospatial performance over time, however probable MCI-LB had a significantly expedited decline in comparison to MCI-AD (**Figure 2**). Possible MCI-LB did not significantly differ in baseline visuospatial performance or rate of decline compared to MCI-AD.

As overall ACE-R memory score is a composite of various tasks; we also examined specific scores to explore memory patterns in-depth. Diagnostic groups did not differ in their registration or un-cued recall of information; performance in these sub-domains was not predicted by age, education, or gender, and did not significantly decline over time. In recognition of learned information, there was a significant difference at baseline between probable MCI-LB, and MCI-AD, with the former performing better in the full model, with an associated improvement in model fit (**Table 4**). Recognition memory did not display any clear time trend overall, nor any group differences in decline.

To explore visuospatial decline more clearly, ACE-R visuospatial totals were decomposed into visuo-constructional (pentagon and cube copying, and clock drawing), and perceptual scores (letter identification and dot-counting), each marked out of eight. There was no significant time trend in visuo-perceptual performance, no effect of age, education, or gender, and no influence of diagnostic status; none of these improved model fit. Visuo-constructional performance was significantly influenced by diagnosis with both main effect and time interaction indicated by improved model fit (**Table 4**); probable MCI-LB performed poorer at baseline, and deteriorated at a faster rate than MCI-AD.After controlling for baseline function post hoc, without interaction with time (as indicated by AIC), the pattern of faster decline in probable MCI-LB remained (Fixed effect estimate for time x diagnosis interaction: $\beta = -0.7$, SE = 0.30, $t(45) = -2.296$, $p = .026$), suggesting that the declining trend was not just an artefact of the lower starting function in probable MCI-LB.

To adequately assess visuo-perception, a secondary model examined line-angle task performance, which showed utility in a previously reported cross-sectional study (21), and was administered repeatedly. Higher values reflect poorer angle discrimination (in degrees) and therefore worse performance. LAT performance was best predicted by the inclusion of diagnosis, without time-interaction (**Table 4**). Genders significantly differed in performance, with males better able to discriminate angle differences than females, but did not differ in their progressions. Probable MCI-LB was associated with significantly poorer angle judgement than MCI-AD at baseline. There was no significant time trend in LAT performance, and no interaction of time with other effects. There were few repeated observations (n = 132), limiting the ability to estimate changes over time.

Repeated measurements were also available for FAS verbal fluency; in the full model, probable MCI-LB had significantly poorer performance at baseline after controlling for covariates (**Table 4**). There was no significant time effect, or interaction with diagnosis. Diagnostic status was retained in the best-fit model. As with the LAT, repeated measures were taken but observations were limited (n = 130).

For TMT-A, completion time was best predicted by models incorporating age and education as non-interacting effects (**Table 4)**; including diagnosis improved fit, but diagnostic effects were non-significant. Completion times progressively slowed over time in the overall group. For TMT-B there was no effect of diagnostic group. In both, higher education was associated with faster- and higher age with slower completion.

Mean and SD of correct response times in both simple and choice reaction tests, and digit vigilance task, were not significantly predicted by age, education, or gender. Incorporating diagnosis did not improve model fits. Reaction times did not clearly improve or worsen over time and there were no differences in profiles or trajectories between the diagnostic groups.

DISCUSSION

There was no clear difference in rates of global cognitive decline between diagnostic subgroups, contrary to our hypothesis, but as hypothesized, probable MCI-LB was associated with a faster deterioration in aspects of visuospatial function as assessed by the ACE-R. We did not observe different rates of decline in attentional or executive functions between groups.

Overall memory performance did not differ between groups, either in initial impairment or decline thereafter. In exploratory analyses MCI-AD displayed poorer recognition memory than probable MCI-LB, but these did not differ in their progressions.

The more severe pattern and trajectory of visuo-constructional impairment in probable MCI-LB aligns with previous findings in dementia (13, 14, 29), Parkinson's disease (32) and MCI (19, 33), and may reflect disruption to cortical (34, 35) and sub-cortical (36) visual systems in DLB. While the ACE-R appears insensitive to visuo-perceptual decline in MCI, group differences are evident at baseline with the line angle discrimination task, suggesting that relatively pure perceptual tests might be valuable in assessing earlier visuospatial impairments in MCI.

Probable MCI-LB did not deteriorate faster in global cognitive function than MCI-AD, consistent with some (9), but not all (4) findings from the respective dementia stages, which did

not support our hypothesis; this could suggest that an accelerated decline occurs in DLB later than at the MCI stage. Alternatively, total score in the ACE-R may not account for global cognitive decline in MCI-LB and MCI-AD equally given their different patterns of domain-specific cognitive impairment; ACE-R sub-scores are not equally weighted towards total score, or equally sensitive to dysfunction, and so may underestimate the relative contributions of some domains to global cognitive impairment. Further exploration may establish whether MCI-LB also has a comparable rate of dementia onset as MCI-AD, or if the faster expected decline manifests in faster loss of independent function after onset of cognitive impairment. Furthermore, our subject numbers are modest, and longer follow-up may be required to identify differences in decline.

These results help resolve some of the previously reported inconsistencies between two different tests of verbal fluency (21); after controlling for relevant covariates and undertaking repeated measurement, ACE-R verbal fluency sub-score and FAS letter-fluency were consistent in finding greater impairments of verbal fluency in probable MCI-LB than in MCI-AD.

It was expected that MCI-LB would be associated with less memory impairment than MCI-AD. This hypothesis was only partially supported; while overall memory scores did not show this pattern, recognition-specific memory was worse in AD than probable MCI-LB. These results partially reflect previously observed patterns of memory impairments in AD and DLB, as assessed with dedicated verbal learning tests (14, 37), with DLB displaying difficulties with encoding and recall but relatively preserved recognition, in comparison with the rapid 'forgetting' associated with AD.

The unexpected lack of progressive decline in memory may be partially explained by floor effects, or repeated practice and familiarity with common screening tests, such as the ACE-R. Comparison with a healthy control cohort may clarify whether practice effects are contributing, and if observed declines in language and attention are related to neurodegenerative processes, or normal aging. This would also afford the opportunity to characterise cognitive profile categorically, for example as amnestic or non-amnestic (19), in comparison to healthy normative data.

Intended for dementia screening, ACE-R sub-scores may be insensitive to domain-specific decline in MCI. More sensitive and less familiar tests may be suitable for this purpose, such as computerized testing batteries. While the RAVLT was administered, there were insufficient repeated observations to develop a longitudinal model; repeated assessment with a suitable memory test may better demonstrate how memory progresses over the course of MCI.

Our findings are from a thoroughly-assessed prospectively-recruited longitudinal MCI cohort, differentiated by clinical diagnostic features, and these results provide important preliminary data on disease-specific patterns of cognitive impairment, and progressions over the course of MCI with LB versus AD. However, as participants were identified based on their reported presence of possible symptoms of DLB, the MCI-AD group may not be entirely representative of the typical presentation of MCI in AD. MCI-AD participants had repeated, detailed clinical assessment and normal FP-CIT scans, but it remains possible that some of these patients could be cases of early DLB, with cognitive impairment preceding the appearance of core clinical features; this is

corroborated by the emergence of LB symptoms in three MCI-AD patients who consequently were diagnosed with possible DLB. There is a need for clinically-classified MCI cases to undergo neuropathological validation of these differential diagnoses.

Using multiple domain-specific tests, these results are limited by the use of independent tests without adjustment for multiple comparisons, and limited improvement of model fit in some domains; there is a need for replication of these findings, and future research with larger samples may benefit from the use of multivariate methods to succinctly describe multi-domain change.

The characteristics of possible MCI-LB remain unclear as they did not differ from MCI-AD in cognitive performance. Given the limited sample size, there may be a lack of statistical power to identify any real differences from MCI-AD or probable MCI-LB. Further exploration may establish how LB symptomology develops over time in this cohort, how this affects progression, and where possible MCI-LB diagnoses fit into this picture, as 'possible' diagnoses may include early-stage low-symptomatic MCI-LB cases, or atypical presentations of MCI-AD such as those with false-positive FP-CIT imaging.

While some MCI cases demonstrate a clear cognitive decline towards dementia over the course of this study, others remain stable for many years; this could be explained by the existence of sub-groups with differing progressions. Specific clinical features, demographics, medical history, or biomarkers may be associated with steeper or flatter trajectories of cognitive decline.

Although differences were found between diagnostic groups in some cognitive domains, in only

a handful of analyses was diagnostic status found to be a valuable predictor of function under the more parsimonious model-fitting criteria.

While the differences between AD and DLB in verbal fluency, visuospatial functions, and recognition memory may already be observed in their respective MCI stages, with visuospatial functions also declining faster in the latter, expected differences in other executive functions, memory encoding and recall, attention, and global decline are not yet apparent at this stage and require further exploration. Repeated testing with appropriately sensitive visuospatial, recognition memory, and fluency tests may therefore be appropriate in the assessment of cognitive decline in MCI-LB.

Author Contributions:

CAH: Analysis, drafting, critical revision, final approvement, agreement to accountability

FEM: Interpretation, critical revision, final approvement, agreement to accountability

PCD: Conception, design, acquisition, critical revision, final approvement, agreement to accountability

JPT: Conception, design, acquisition, critical revision, final approvement, agreement to accountability

JOB: Conception, interpretation, critical revision, final approvement, agreement to accountability

NB: Acquisition, critical revision, final approvement, agreement to accountability

KO: Acquisition, critical revision, final approvement, agreement to accountability

JL: Design, acquisition, critical revision, final approvement, agreement to accountability

GP: Design, acquisition, critical revision, final approvement, agreement to accountability

IGM: Conception, design, interpretation, critical revision, final approvement, agreement to accountability

AJT: Conception, design, acquisition, interpretation, critical revision, final approvement, agreement to accountability

REFERENCES

1. Vann Jones SA,O'Brien JT: The prevalence and incidence of dementia with Lewy bodies: a systematic review of population and clinical studies. Psychol. Med. 2014; 44:673-683

2. McKeith IG, Boeve BF, Dickson DW, et al: Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology 2017; 89:88-100

3. Gurnani AS,Gavett BE: The differential effects of Alzheimer's disease and Lewy Body pathology on cognitive performance: A meta-analysis. Neuropsychol. Rev. 2017; 27:1-17

4. Rongve A, Soennesyn H, Skogseth R, et al: Cognitive decline in dementia with Lewy bodies: a 5-year prospective cohort study. BMJ Open 2016; 6:e010357

5. Mueller C, Soysal P, Rongve A, et al: Survival time and differences between dementia with Lewy bodies and Alzheimer's disease following diagnosis: A meta-analysis of longitudinal studies. Ageing Res Rev 2019; 50:72-80

6. Mueller C, Perera G, Rajkumar AP, et al: Hospitalization in people with dementia with Lewy bodies: Frequency, duration, and cost implications. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 2018; 10:143-152

7. Lee DR, McKeith I, Mosimann U, et al: Examining carer stress in dementia: the role of subtype diagnosis and neuropsychiatric symptoms. Int. J. Geriatr. Psychiatry 2013; 28:135-141

8. Boström F, Jönsson L, Minthon L, et al: Patients with Lewy body dementia use more resources than those with Alzheimer's disease. Int. J. Geriatr. Psychiatry 2007; 22:713-719

9. Walker Z, McKeith I, Rodda J, et al: Comparison of cognitive decline between dementia with Lewy bodies and Alzheimer's disease: a cohort study. BMJ Open 2012; 2:e000380

10. McKhann GM, Knopman DS, Chertkow H, et al: The diagnosis of dementia due to Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s

Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia 2011; 7:263-269

11. Scheltens P, Leys D, Barkhof F, et al: Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. J. Neurol. Neurosurg. Psychiatry 1992; 55:967-972

12. Han SD, Nguyen CP, Stricker NH, et al: Detectable neuropsychological differences in early preclinical Alzheimer's disease: A meta-analysis. Neuropsychol. Rev. 2017; 1-21

13. Metzler-Baddeley C: A review of cognitive impairments in dementia with Lewy bodies relative to Alzheimer's disease and Parkinson's disease with dementia. Cortex 2007; 43:583-600

14. Ferman TJ, Smith GE, Boeve BF, et al: Neuropsychological differentiation of dementia with Lewy bodies from normal aging and Alzheimer's disease. Clin Neuropsychol 2006; 20:623-636

15. Ballard CG, Ayre G, O'Brien J, et al: Simple standardised neuropsychological assessments aid in the differential diagnosis of dementia with Lewy bodies from Alzheimer's disease and vascular dementia. Dement. Geriatr. Cogn. Disord. 1999; 10:104-108

16. Barber R, Gholkar A, Scheltens P, et al: Medial temporal lobe atrophy on MRI in dementia with Lewy bodies. Neurology 1999; 52:1153-1158

17. Albert MS, DeKosky ST, Dickson D, et al: The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia 2011; 7:270-279

18. Lambon Ralph MA, Patterson K, Graham N, et al: Homogeneity and heterogeneity in mild cognitive impairment and Alzheimer's disease: a cross-sectional and longitudinal study of 55 cases. Brain 2003; 126:2350-2362

19. Ferman TJ, Smith GE, Kantarci K, et al: Nonamnestic mild cognitive impairment progresses to dementia with Lewy bodies. Neurology 2013; 81:2032-2038

20. Visser P, Verhey F, Hofman P, et al: Medial temporal lobe atrophy predicts Alzheimer's disease in patients with minor cognitive impairment. J. Neurol. Neurosurg. Psychiatry 2002; 72:491-497

21. Donaghy PC, Taylor J-P, O'Brien JT, et al: Neuropsychiatric symptoms and cognitive profile in mild cognitive impairment with Lewy bodies. Psychol. Med. 2018; 48:2384-2390

22. Kemp J, Philippi N, Phillipps C, et al: Cognitive profile in prodromal dementia with Lewy bodies. Alzheimers Res. Ther. 2017; 9:19

23. Génier Marchand D, Postuma RB, Escudier F, et al: How does dementia with Lewy bodies start? prodromal cognitive changes in REM sleep behavior disorder. Ann. Neurol. 2018; 83:1016-1026

24. Thomas AJ, Donaghy PC, Roberts G, et al: Diagnostic accuracy of dopaminergic imaging in prodromal dementia with Lewy bodies. Psychol. Med. 2019; 49:396-402

25. Román GC, Tatemichi TK, Erkinjuntti T, et al: Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. Neurology 1993; 43:250-250

26. Rascovsky K, Hodges JR, Knopman D, et al: Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 2011; 134:2456-2477

27. McKeith IG, Dickson DW, Lowe J, et al: Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005; 65:1863-1872

28. O'Brien JT, Colloby S, Fenwick J, et al: Dopamine transporter loss visualized with FP-CIT SPECT in the differential diagnosis of dementia with Lewy bodies. Arch. Neurol. 2004; 61:919-925

29. Wood JS, Firbank MJ, Mosimann UP, et al: Testing visual perception in dementia with Lewy bodies and Alzheimer disease. Am J Geriatr Psychiatry 2013; 21:501-508

30. Bates D, Mächler M, Bolker B, et al: Fitting linear mixed-effects models using lme4. Journal of Statistical Software 2015; 67:1-48

31. Kuznetsova A, Brockhoff PB,Christensen RHB: lmerTest package: tests in linear mixed effects models. Journal of Statistical Software 2017; 82:1-26

32. Weil RS, Schrag AE, Warren JD, et al: Visual dysfunction in Parkinson’s disease. Brain 2016; 139:2827-2843

33. Yoon JH, Kim M, Moon SY, et al: Olfactory function and neuropsychological profile to differentiate dementia with Lewy bodies from Alzheimer's disease in patients with mild cognitive impairment: a 5-year follow-up study. J. Neurol. Sci. 2015; 355:174-179

34. Minoshima S, Foster NL, Sima AAF, et al: Alzheimer's disease versus dementia with Lewy bodies: cerebral metabolic distinction with autopsy confirmation. Ann. Neurol. 2001; 50:358-365

35. Fujishiro H, Iseki E, Kasanuki K, et al: A follow up study of non-demented patients with primary visual cortical hypometabolism: Prodromal dementia with Lewy bodies. J. Neurol. Sci. 2013; 334:48-54

206 36. Delli Pizzi S, Maruotti V, Taylor J-P, et al: Relevance of subcortical visual pathways
207 disruption to visual symptoms in dementia with Lewy bodies. Cortex 2014; 59:12-21
208 37. Salmon DP, Galasko D, Hansen LA, et al: Neuropsychological deficits associated with
209 diffuse Lewy body disease. Brain Cogn. 1996; 31:148-165
210

FIGURE LEGENDS

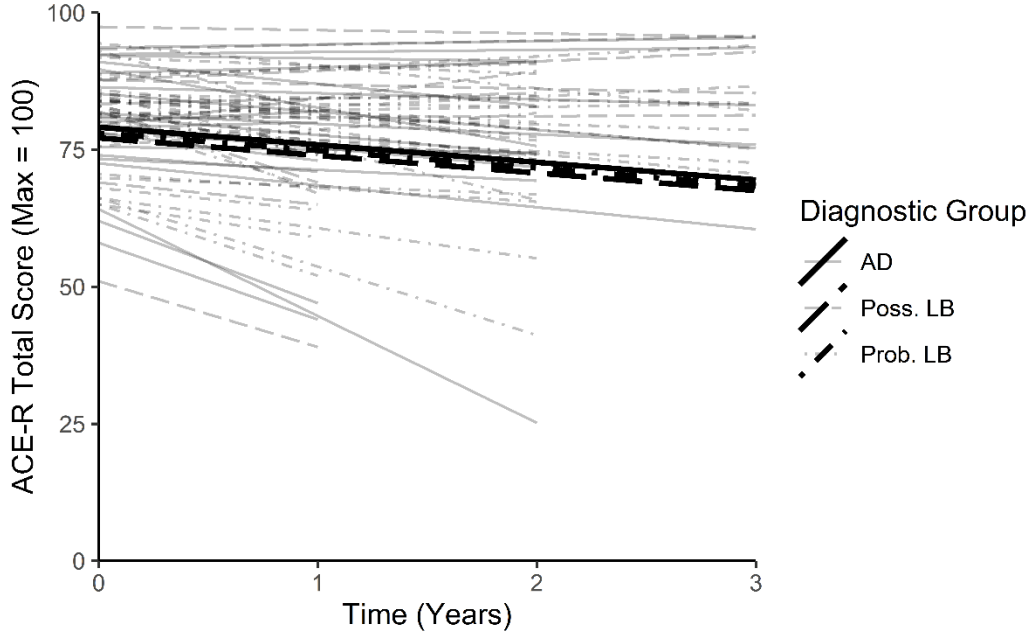

Figure 1. ACE-R total score trajectories in individuals and clinically-defined mild cognitive impairment (MCI) subgroups

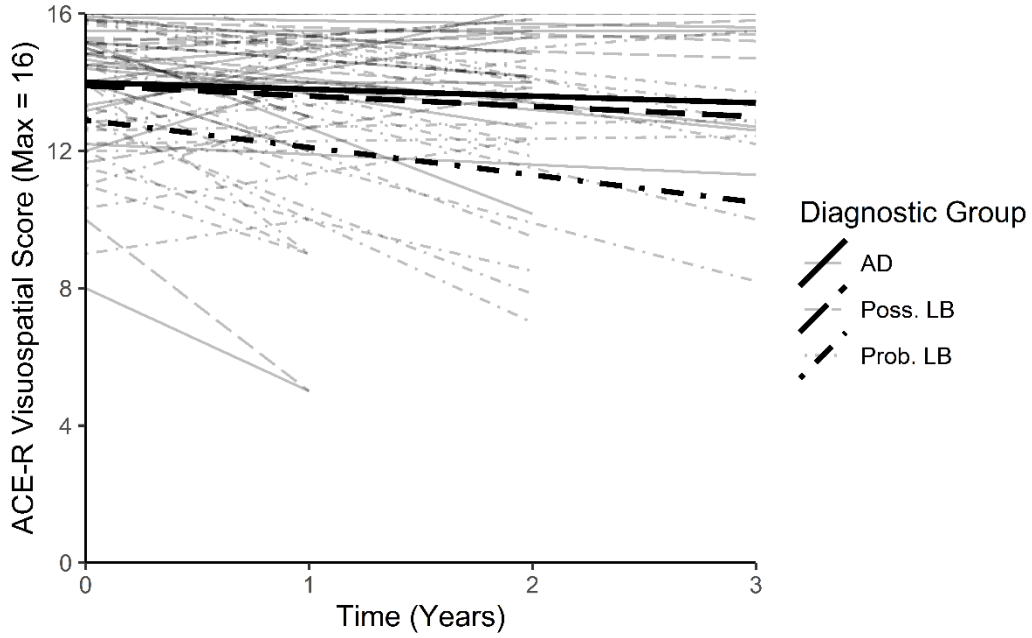

Figure 2. ACE-R visuospatial function trajectories in individuals and clinically-defined mild cognitive impairment (MCI) subgroups

Table 1. Baseline demographic, clinical, and cognitive information for MCI subgroups: count (%) for frequency data; mean (SD) or median (IQR) for scales; omnibus test *p* value

Demographics and clinical measures	MCI-AD	Poss. MCI-LB	Prob. MCI-LB	*p*
N	23	12	41	-
Female	15 (65%)	5 (42%)	14 (34%)	.055
Male	8 (35%)	7 (58%)	27 (66%)	-
Age	78.2 (7.5)	75.3 (7.3)	75.5 (7.6)	.335
Years in Education	11.9 (3.0)	10.8 (2.1)	11.4 (2.8)	.531
CDR Total (0-3), Median	0.5 (0)	0.5 (0)	0.5 (0)	.206
IADL Total (0-8)	7.2 (0.9)	6.6 (1.6)	6.1 (1.7)	.038
CIRS-G Total (0-56)	9.2 (4.0)	12.1 (5.2)	9.1 (4.1)	.097
MSQ Q1 'Yes'	3 (13%)	2 (17%)	20 (49%)	.095
ESS (0-24)	4.2 (3.7)	6.8 (4.9)	10.4 (5.0)	<.001
GDS (0-15)	2.4 (2.2)	2.9 (2.7)	4.4 (3.6)	.039
UPDRS-III (4-73)	15.0 (7.1)	14.0 (7.8)	26.2 (16.2)	.001
NPI Total (0-144)	5.8 (7.0)	12.9 (13.2)	13.7 (9.8)	.021
NEVHI (0-30)	1.0 (2.8)	1.3 (3.4)	3.4 (4.4)	.031
CAF (0-16)	0.3 (1.0)	2.0 (2.5)	2.4 (2.9)	.019
DCFS (4-20)	5.6 (1.6)	7.4 (2.3)	8.9 (3.2)	<.001
Lost Sense of Smell	4 (17%)	2 (17%)	19 (46%)	.026
Cognitive measures				
MMSE (0-30)	26.5 (2.3)	26.2 (2.9)	26.5 (2.0)	.901
ACE-R Total (0-100)	79.5 (11.70)	79.3 (14.1)	79.3 (8.3)	.996
ACE-R Att./Orient. (0-18)	17.0 (1.4)	16.6 (2.1)	16.8 (1.4)	.745

ACE-R Memory (0-26)	15.7 (5.8)	15.8 (5.9)	17.4 (4.4)	.356
ACE-R Fluency (0-14)	9.7 (2.7)	8.2 (3.3)	7.9 (2.8)	.041
ACE-R Language (0-26)	22.9 (3.3)	24.1 (2.9)	23.6 (2.1)	.385
ACE-R Visuospatial (0-16)	14.2 (1.9)	14.7 (1.9)	13.5 (2.1)	.125
FAS Fluency (0+)	36.2 (13.1)	26.5 (16.3)	29.0 (14.5)	.093
Rey Delayed Recall (0-15)	3.1 (4.3)	2.5 (2.6)	3.9 (3.1)	.438
Rey Recognition (0-15)	12.0 (2.3)	10.3 (3.6)	11.7 (2.3)	.184
Rey % Trial 5 Recalled	35.2 (39.0)	37.5 (40.0)	53.9 (50.6)	.253
GNT (0-30)	16.5 (6.8)	20.3 (5.9)	17.6 (5.7)	.223
TMT-A Time (seconds)	67 (40)	47 (21)	73 (36)	.104
TMT-B Time (seconds)	152 (83)	153 (109)	165 (94)	.897
SRT Mean (ms)	406 (149)	410 (177)	403 (155)	.993
CRT Mean (ms)	678 (131)	747 (355)	730 (250)	.642
DVT Mean (ms)	555 (75)	534 (72)	584 (72)	.074
LAT Discrimination (°)	18 (13)	14 (8.7)	26 (16)	.026
Motion Task Score (max 1)	0.70 (0.28)	0.67 (0.28)	0.65 (0.28)	.784

Gender, MSQ Q1, Question 1 of the Mayo Sleep Questionnaire "Have you ever seen the patient appear to "act out his/her dreams" while sleeping? (punched or flailed arms in the air, shouted or screamed)", Lost Sense of Smell, self-reported in clinical interview, Chi-squared test, df = 2; Age, Years in Education, CIRS-G, Cumulative Illness Rating Scale for Geriatrics, MMSE, Mini-Mental State Examination, ACE-R total and sub-tests, Addenbrooke's Cognitive Examination – Revised, Att./Orient., Attention & Orientation, GNT, Graded Naming Test, ANOVA F-test, df = 2, 73;

CDR Total, Clinical Dementia Rating Total, Kruskal-Wallis Chi-squared test, df = 2;

IADL, Instrumental Activities of Daily Living, ANOVA F-test, df = 2, 65, Tukey HSD-corrected multiple comparisons: Possible MCI-LB vs. MCI-AD p = .588, Probable MCI-LB vs. MCI-AD p = .031;

ESS, Epworth Sleepiness Scale, ANOVA F-test, df = 2, 73, Tukey HSD-corrected multiple comparisons: Possible MCI-LB vs. MCI-AD p = .244, Probable MCI-LB vs. MCI-AD p < .001;
GDS, Geriatric Depression Scale, ANOVA F-test, df = 2, 73, Tukey HSD-corrected multiple comparisons: Possible MCI-LB vs. MCI-AD p = .901, Probable MCI-LB vs. MCI-AD p = .041;
UPDRS, Unified Parkinson's Disease Rating Scale – Part III, ANOVA F-test, df = 2, 73, Tukey HSD-corrected multiple comparisons: Possible MCI-LB vs. MCI-AD p = .972, Probable MCI-LB vs. MCI-AD p = .004;
NPI, Neuropsychiatric Inventory, ANOVA F-test, df = 2, 65, Tukey HSD-corrected multiple comparisons: Possible MCI-LB vs. MCI-AD p = .150, Probable MCI-LB vs. MCI-AD p = .017;
NEVHI, North-East Visual Hallucinations Inventory, ANOVA F-test, df = 2, 73, Tukey HSD-corrected multiple comparisons: Possible MCI-LB vs. MCI-AD p = .957, Probable MCI-LB vs. MCI-AD p = .038;
CAF, Clinician Assessment of Fluctuation, ANOVA F-test, df = 2, 65, Tukey HSD-corrected multiple comparisons: Possible MCI-LB vs. MCI-AD p = .202, Probable MCI-LB vs. MCI-AD p = .014;
DCFS, Dementia Cognitive Fluctuation Scale, ANOVA F-test, df = 2, 65, Tukey HSD-corrected multiple comparisons: Possible MCI-LB vs. MCI-AD p = .216, Probable MCI-LB vs. MCI-AD p < .001;

ACE-R Fluency, Tukey HSD-corrected multiple comparisons: Possible MCI-LB vs. MCI-AD p = .270, Probable MCI-LB vs. MCI-AD p = .033;

Rey Auditory Verbal Learning Test Delayed Recall, Recognition, % Trial 5 Recalled, TMT-A, Trailmaking Test Part A, ANOVA F-test, df = 2, 71;

TMT-B, Trailmaking Test Part B, ANOVA F-test, df = 2, 44;

SRT, Simple Reaction Task, CRT, Choice Reaction Task, DVT, Digit Vigilance Task, Motion Task, ANOVA F-test, df = 2, 72.

LAT, Line Angle Task, ANOVA F-test, df = 2, 66, Tukey HSD-corrected multiple comparisons: Possible MCI-LB vs. MCI-AD p = .733, Probable MCI-LB vs. MCI-AD p = .116.

Table 2. Baseline DLB clinical feature presence in diagnostic groups.

	MCI-AD	Poss. MCI-LB	Prob. MCI-LB
Parkinsonism	0 (0%)	0 (0%)	19 (46%)
Cognitive Fluctuations	0 (0%)	4 (33%)	23 (56%)
REM Sleep Behaviour Disorder	0 (0%)	5 (42%)	20 (49%)
Complex Visual Hallucinations	0 (0%)	0 (0%)	12 (29%)
Abnormal FP-CIT SPECT	0 (0%)	3 (25%)	26 (67%)[a]

[a]*Two participants did not consent to FP-CIT SPECT, but had sufficient clinical symptomology to receive a probable MCI-LB diagnosis without confirmatory biomarkers*

Table 3. Fixed effect coefficient estimates for best fit and full models (including diagnostic group, interacting with time where appropriate) for ACE-R total score and domain sub-scores

ACE-R Total	**Intercept**[+]	**Change from intercept**					*Time*	*Interaction with time*	
	MCI-AD	**Possible MCI-LB**	**Probable MCI-LB**	**Education**	**Age**	**Gender Male**	*MCI-AD*	*Possible MCI-LB*	*Probable MCI-LB*
Best fit	83.4 (10.60); **46, < .001**	No difference from MCI-AD		0.6 (0.31); 63, **.041**	-0.15 (0.13); 48, .257	-0.4 (1.96); 45, .856	-3.2 (0.55); **38, < .001**	No difference from MCI-AD	
Full model	85.3 (11.25); **50, < .001**	-2.0 (2.97); 42, .500	-1.1 (2.25); 45, .630	0.6 (0.32); 62, .064	-0.16 (0.13); 51, .243	-0.05 (2.06); 46, .981	-3.2 (0.55); **38, < .001**	No difference from MCI-AD	
ACE-R Attention & Orientation									
Best fit	16.1 (1.91); **90, < .001**	No difference from MCI-AD		0.06 (0.06); 98, .292	0.001 (0.02); 88, .961	-0.2 (0.35); 90, .623	-1.2 (0.19); **44, < .001**	No difference from MCI-AD	
Full model	16.3 (2.0); **87, < .001**	-0.3 (0.53); 87, .616	-0.2 (0.40); 88, .686	0.06 (0.06); 96, .349	0.00005 (0.02); 86, .999	-0.1 (0.37); 88, .721	-1.5 (0.19); 44, < **.001**	No difference from MCI-AD	
ACE-R Memory									
Best fit	22.6 (6.60); 74, **.001**	No difference from MCI-AD		0.2 (0.18); 115, .397	-0.1 (0.08); 71, .189	0.4 (1.21); 73, .756	-0.1 (0.22); 54, .807	No difference from MCI-AD	
Full model	21.2 (6.83); 73, **.003**	0.4 (1.81); 70, .810	1.6 (1.36); 70, .251	0.2 (0.19); 115, .353	-0.1 (0.08); 69, .222	0.01 (1.26); 71, .991	-0.1 (0.22); 55, .785	No difference from MCI-AD	
ACE-R Verbal Fluency									

Best fit	8.8 (3.56); 73, **.015**	-0.9 (0.95); 70, .322	-1.5 (0.71); 71, **.032**	0.3 (0.10); 111, **.004**	-0.04 (0.04); 70, .403	-0.2 (0.66); 71, .734	-0.2 (0.12); 81, **.015**	No difference from MCI-AD	
ACE-R Language									
Best fit	26.3 (3.05); **70, < .001**	No difference from MCI-AD		0.15 (0.09); 106, .088	-0.06 (0.04); 69, .110	-0.04 (0.56); 70, .942	-0.5 (0.14); 46, < **.001**	No difference from MCI-AD	
Full model	25.4 (3.14); **69, < .001**	1.3 (0.83); 65, .130	0.5 (0.63); 68, .465	0.18 (0.09); 101, .051	-0.06 (0.04); 67, .134	-0.2 (0.58); 67, .716	-0.5 (0.14); 44, < **.001**	No difference from MCI-AD	
ACE-R Visuospatial									
Best fit	12.8 (2.72); **68, < .001**	-0.04 (0.72); 67, .955	-1.0 (0.54); 67, .081	0.1 (0.08); 86, .130	-0.003 (0.03); 68, .933	0.7 (0.50); 67, .166	-0.2 (0.23); 38, .420	-0.1 (0.37); 30, .830	-0.6 (0.28); 34, **.036**

[+] *Unstandardized coefficient (SE); t-statistic degrees of freedom, p value*

Table 4. Fixed effect coefficient estimates for ACE-R visuo-construction and recognition memory sub-scores, line angle discrimination task (LAT; °) and executive function tests; Trail Making Test completion times (seconds) and FAS total score (number of words generated)

	Intercept[+]			**Change from intercept**			*Time*	*Interaction with time*	
ACE-R Visuo-Construction	**MCI-AD**	**Possible MCI-LB**	**Probable MCI-LB**	**Education**	**Age**	**Gender Male**	*MCI-AD*	*Possible MCI-LB*	*Probable MCI-LB*
Best fit	5.3 (2.29); **71, .024**	0.3 (0.61); 68, .623	-0.9 (0.46); 69, **.045**	0.1 (0.07); 88, .134	-0.004 (0.03); 69, .875	0.8 (0.42); 70, .054	-0.1 (0.19); 36, .713	-0.1 (0.31); 32, .739	-0.6 (0.24); 36, **.018**
ACE-R Recognition Memory									
Best fit	3.5 (1.13); 63, **.003**	0.0 (0.29); 63, .993	0.5 (0.22); **66, .035**	0.1 (0.03); 74, .108	-0.01 (0.01); 63, .670	-0.1 (0.21); 64, .759	0.1 (0.07); 18, .429	No difference from MCI-AD	
LAT									
Best fit	32.9 (18.58); 68, .081	-4.5 (4.92); 70, .360	9.9 (3.66); **71, .008**	-0.9 (0.56); 71, .120	-0.01 (0.22); 69, .971	-9.9 (3.41); 72, **.005**	3.0 (2.17); 26, .178	No difference from MCI-AD	
TMT-A									
Best fit	-54.2 (41.67); 66, .198	-21.7 (10.85); 64, .050	2.3 (8.23); 66, .785	-3.9 (1.23); 69, **.002**	2.1 (0.50); 65, <**.001**	15.4 (7.56); 65, **.046**	13.0 (5.15); 32, **.017**	No difference from MCI-AD	
TMT-B									
Best fit	-72.1 (105.60); 44, .498	No difference from MCI-AD		-12.8 (3.30); 53, <**.001**	4.9 (1.30); 46, <**.001**	31.9 (19.72); 46, .113	6.1 (6.28); 36, .341	No difference from MCI-AD	
Full model	-98.0 (112.2); 43, .387	2.6 (26.91); 41, .922	18.4 (22.99); 40, .428	-12.2 (3.42); 52, <**.001**	5.0 (1.33); 44, <**.001**	28.0 (20.59); 42, .181	5.7 (6.28); 35, .374	No difference from MCI-AD	
FAS Total									

Best fit	14.4 (16.91); 69, .399	No difference from MCI-AD		2.2 (0.50); **93, < .001**	-0.1 (0.20); 69, .605	-1.4 (3.12); 70, .662	0.2 (0.68); 69, .725	No difference from MCI-AD
Full model	24.2 (17.05); 68,.160	-9.0 (4.50); 68, .050	-7.2 (3.40); 69, **.037**	2.0 (0.49); 91, <**.001**	-0.2 (0.20); 67, .439	0.5 (3.15); 68, .879	0.3 (0.67); 70, .688	No difference from MCI-AD

289 [+]*Unstandardized coefficient (SE); t-statistic degrees of freedom, p value*

290