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Research Report

RATES OF DECLINE DISTINGUISH ALZHEIMER'S DISEASE AND MILD COGNITIVE IMPAIRMENT RELATIVE TO NORMAL AGING: INTEGRATING COGNITION AND BRAIN FUNCTION

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Aims: Increasing age is the strongest risk factor for Alzheimer's disease (AD). Yet, departure from normal age-related decline for established markers of AD including memory, cognitive decline and brain function deficits, has not been quantified.

Methods: We examined the cross-sectional estimates of the "rate of decline" in cognitive performance and psychophysiological measures of brain function over age in AD, preclinical (subjective memory complaint-SMC, Mild Cognitive Impairment-MCI) and healthy groups. Correlations between memory performance and indices of brain function were also conducted.

Results: The rate of cognitive decline increased between groups: AD showed advanced decline, and SMC/MCI groups represented intermediate stages of decline relative to normal aging expectations. In AD, advanced EEG alterations (excessive slow-wave/reduced fast-wave EEG, decreased working memory P450 component) were observed over age, which were coupled with memory decline. By contrast, MCI group showed less severe cognitive changes but specific decreases in the working memory N300 component and slow-wave (delta) EEG, associated with decline in memory.

Discussion and Integrative Significance: While the cognitive data suggests a continuum of deterioration associated with increasing symptom severity across groups, integration with brain function measures points to possible distinct compensatory strategies in MCI and AD groups. An integrative approach offers the potential for objective markers of the critical turning point, with age as a potential factor, from mild memory problems to disease.

Keywords: Alzheimer's disease (AD); Mild Cognitive Impairment (MCI); Subjective Memory Complaint (SMC); normal aging; cognition; EEG; working memory; integrative neuroscience.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative dementia which has severe debilitating consequences. AD is characterized by progressive cognitive deficits in memory [66], and associated problems in language and executive functions [14, 5]. Social cognitive functions also decline in AD, along with an increase in negative mood [7]. Corresponding alterations in baseline brain function, indexed by electroencephalography (EEG) [47], and in event-related potentials (ERPs) elicited by

cognitive activation tasks have also been observed [49]. These alterations may reflect a loss of gray matter, and interconnections between neurons at both macro- and microscopic scales [9].

A similar, albeit less severe, decline in memory and associated brain function measures is also characteristic of normal aging [20, 31, 68]. For instance, memory along with executive functions and attention deteriorate linearly after about 50 years of age [20]. In normal aging, however, there is a preseveration or even improvement in social/emotional cognition [77], and evidence that crystallized intelligence abilities increase across age [17]. The frontal aging hypothesis suggests that selective deterioration within frontal regions of the brain observed through the processes of normal aging, underpins the decline in the specific cognitive abilities that are dependent on the integrity of the frontal lobes [22]. This hypothesis is largely supported by morphological studies indicating that structural changes are more apparent within frontal regions in normal aging, in contrast to more focal degeneration over temporal regions prior to and during the progression of dementia [58]. This underlies the popular argument that AD involves distinct processes from those observed in normal aging [9, 54]. While the frontal aging hypothesis probably explains a good deal of age-related changes in cognition, growing evidence suggests the hypothesis is oversimplified, and that age effects broader neural networks ([36], p. 126) including temporal regions [41] and integrated systems of the brain on a global scale (for review, see [35]). Further, there is growing evidence that the relationship between normal aging and AD-related changes could be considered on a continuum [76]. Given current evidence, it is likely that the mechanisms underpinning cognitive decline in aging versus AD are only partially distinct [75]. For instance, the influential cholinergic hypothesis suggests that changes to acetylcholine functioning and other cholinergic system abnormalities, contribute to normal cognitive decline and EEG alterations as well as to Alzheimer's disease [23, 65, 71]. Adding weight to these arguments is the premise that age is the strongest risk factor for Alzheimer's disease, despite the complex array of genetic and environmental factors that have also been implicated [9, 67].

Given these equivocal theoretical issues, the relationship between functional decline observed in normal aging and in dementia is far from resolved, and few studies have reported rates of change across age. The main objective of this study was to determine whether a distinct rate of decline characterizes the progression to AD from a cross-sectional perspective. Firstly, we explored the proposal that the functional deterioration, particularly memory function, observed in AD is a quantitatively more severe expression of the normal aging trajectory. From this view, Subjective Memory Complaint (SMC) and Mild Cognitive Impairment (MCI) conditions that are considered prodromal syndromes in the development of AD, may be characterized by increasingly sharp rates of decline in cognition (particularly memory) and brain function. Using a cross-sectional design, we aimed to capture the rate of deterioration across cognitive and EEG/ERP measures in normal aging relative to SMC, MCI and AD. Secondly, while we predicted that there may be a quantitative decline in cognitive functioning (with a focus on memory) across groups, we also

predicted that such a decline may be supported by partially distinct neural mechanisms. We examined this from an electrophysiological perspective in the current study, and observed the interaction between memory ability and resting state EEG and cognitive ERPs.

SMC, and to a greater extent, MCI, represent conditions where there is higher risk of developing dementia relative to the normal population [28, 57], although importantly, not all these individuals will develop dementia. Individuals with MCI convert to AD at a rate of 10–12% each year [61] (with higher rates noted in other studies [57]), whereas the conversion rate in the normal population is below 1% [9]. There are multiple sub-types of MCI now documented, with "amnestic" MCI being particularly identified as predictive of AD [60]. Amnestic-MCI is characterized by isolated cognitive deficits in memory capacity [61], although current diagnostic criteria for MCI renders it difficult to clinically distinguish amnestic and non-amnestic sub-types [64], Decreased performance on memory tasks have been reported as good predictors of conversion from MCI to AD [24], although it is noted that separation of measures of memory ability from diagnostic indicators is difficult [73], and other studies have reported contrary findings [43]. Changes in patterns of brain activity and structural abnormalities have also been observed preclinically [10]. SMC is a possible preclinical stage of dementia, particularly when other cognitive deficits are also apparent [1, 69].

Elucidating relative rates of decline may offer a step towards addressing one of the major problems facing geriatric neurology: how to identify when the increased risk for dementia onset becomes critical in patients with MCI, or even SMC [24]. The search for objective markers of AD development is an important goal, given that current clinical assessments such as the Mini Mental State Examination (MMSE) are not consistently sensitive to impairments, and are therefore not reliable prognostic indicators of dementia progression [72]. An integrative neuroscience framework may reveal objective markers of the conversion to dementia from the preclinical MCI condition, which cannot be identified by focusing on single measures in isolation [10]. When considered in isolation, cognitive markers are typically not sufficient for distinguishing those who will develop dementia versus those who will not [5, 55, 72]. There is also a distinct lack of reliable individual biological markers for identifying AD. For instance, direct measures of neural function such as neuroimaging, may not distinguish changes that occur as a result of normal aging from changes in AD when used in isolation [24].

The integration of cognitive with electrophysiological measures of brain function, may offer a more sensitive way to distinguish differential deterioration across preclinical and dementia phases of Alzheimer's disease [62, 74]. While resting EEG power across the entire spectra decreases in normal aging [4, 12, 13, 18], longitudinal and cross-sectional studies suggest that the ratio of slow-wave (delta, theta bands) to fast-wave (alpha, beta bands) power actually increases in the progression toward dementia [25, 47], a pattern which has not been found in MCI subjects [40]. Moreover, a relative increase in slow wave/decrease in fast-wave EEG activity is a sign of

decreased performance capacity and the onset of neuropathology [44]. Indeed, EEG changes have been associated with a wide range of cognitive functions in Alzheimer's disease [8, 74]. Evidence that such EEG markers may predict those with MCI who develop AD [40, 42] suggests EEG markers could be important in distinguishing AD from prodromal phases. In addition, the inclusion of EEG with cognitive measures has been found to be critical in predicting AD from other dementia sub-types [47]. ERPs may add to the sensitivity with which the progression to AD might be identified. For instance, the P300 generated in a working memory paradigm is significantly more reduced in AD [2, 8] than it is with normal aging [52].

In this study, we charted the relative rates of decline in AD, prodromal conditions of MCI and SMC, compared to those expected for normal aging across cognitive, EEG and ERP modalities. We were able to harness the power of a large standardized database (Brain Resource International Database — BRID), in order to examine the patterns expected across the life span in normal individuals. Within a cross-sectional design, it was predicted that key cognitive, EEG and ERP measures would distinguish AD and preclinical phases of dementia, relative to normal aging [60]. Specifically, it was predicted that a profile indicating a particularly marked decline in verbal and working memory performance, along with excessive slow-wave/reduced faster-wave EEG and reduced cognitive ERPs would distinguish AD, while the prodromal groups would reveal quantitatively less decline (from MCI to SMC), relative to normal aging. Within this quantitative spectrum of decline, it was also predicted that AD would be distinguished by a specific pattern of associations between cognition and brain function relative to both prodromal and normal aging groups. We focused on the absolute deficits in cognition and brain function in each group, and in addition calculated the rate of change based on the expected slope of aging for each group. This descriptive statistical measure represented the cross-sectional estimate of the rate of decline for each group.

2. Methods

2.1. *Participants*

A total of 76 SMC, 20 MCI and 19 AD subjects, as well as 1008 healthy controls subjects participated as part of the Brain Resource International Database (BRID; www.brainresource.com) [30, 31].

Healthy control subjects were selected to represent a large age range in order to model the changes encompassing cognitive and brain function measures across the life span (age range: 6–80 yrs, mean age = 31.63 yrs, SD = 18.68; 49.9% female). Control subjects were subject to rigorous screening, where exclusion criteria included personal or family history of psychiatric illness, physical brain injury, neurological disorders, and a personal history of drug or alcohol addictions. Healthy controls subjects were tested at multi-sites using standardized BRID data acquisition and testing protocols [31], including Sydney, Adelaide and Melbourne, Australia; New York and

Rhode Island, USA; Nijmegen, The Netherlands. The validity and reliability of the cognitive and EEG/ERP measures has been established [59, 78], as have the age-related norms [20].

The MCI and AD subjects were recruited as part of an ongoing study. The 19 AD participants (age range: 58–95 yrs, mean age = 76.61, SD = 8.72; 55% female) were diagnosed with probable AD according to DSM-IV criteria by a referring neurologist. Subjects were tested on an average of 45 months (SD 21 months) after their first consultation with a neurologist. Standard clinical assessments were conducted on half of the subjects. Clinical Dementia Rating (CDR) [56] scores were 1.0 or 2.0 (average 1.4, SD: 0.5, range 1–2, $n = 8$). Additionally, a subset of the AD subjects scored an average of 20.38 (SD: 4.5; range 16–27, $n = 10$), on the Mini-Mental State Examination (MMSE) [21]. Based on CDR scores, the severity range of this group was moderate to severe, and the majority of subjects are late-onset AD. More focused analyses regarding differences in performance and psychophysiological measures accounted for by severity of AD, and other factors such as early/late onset of AD, will be further elucidated as part of an ongoing study, and will not be addressed here.

The 20 MCI subjects (age range: 54–85 yrs, mean age = 73.6, SD = 9.22; 50% female) were referred by a clinician and diagnosed with MCI according to a Clinical Dementia Rating score of 0.5, administered by a trained research assistant. The MCI sample scored an average of 27.15 (SD: 1.6) on the MMSE (range: 24–30). Given that current diagnostic criteria for MCI necessitates heterogeneity, both amnestic and non-amnestic MCI subjects were included in this study [64].

The 76 subjects in the SMC cohort (age range: 52–88 yrs; mean age = 64.92, SD = 8.45; 59.2% female) have been previously described [1]. Also, subject to the same exclusion criteria outlined above, inclusion criteria included age of 52 years or older, subjective complaint of memory difficulties that had been increasing over time without impacting on normal daily activities or social functioning, and verification from a family member that the subject had displayed evidence of having been experiencing memory problems. All SMC subjects were tested in the BRC lab in Nijmegen, The Netherlands. These subjects scored an average of 27.43 on the MMSE (SD: 1.73, range: 22–30).

All participants were asked to refrain from caffeine or nicotine intake for at least 2 hours prior to testing. All participants gave informed written consent in accordance with human medical research ethical requirements, in collaboration with their caregivers and guardians if required.

2.2. *Design, procedure and data acquisition*

2.2.1. *Neuropsychological battery*

Participants completed a standardized battery of cognitive tests, "IntegNeuro". The cognitive tests were administered in a sound attenuated room via a touchscreen

computer (NEC MultiSync LCD 1530V) with attached headset with a microphone, enabling the tasks to be completed easily by participants even without computer skills. Instructions were delivered visually and audibly, and practice tasks ensured subjects' were able to complete the tasks. Responses were recorded either via the computer (reaction time, accuracy information) or via the microphone (sound files in verbal memory tasks for instance).

The cognitive tests are reliable and valid [59, 78]. Age, sex, and education norms have also been established [20].

All participants were administered the entire battery of neuropsychological tests, but for the purposes of this study, only selected tests were included in the analysis. The selected tests were: Verbal Recall and Learning, Digit Span, Span of Visual Memory, Choice Reaction Time, Verbal Interference, Switching of Attention, Word Generation, Spot-the-word and a motor tapping task. These tests were selected as the most pertinent tests to capture the cognitive dysfunction associated with Alzheimer's disease, as outlined in the introduction, and represent the spectrum of cognitive domains encompassing memory, verbal, attention, sensori-motor and executive function measures [78]. Details of these tests have been published elsewhere [20, 59, 78], and a summary is presented in Table 1. SMC participants did not complete tests of verbal processing (i.e., word fluency and spot-the-word).

2.2.2. *Resting EEG*

Electroencephalogram (EEG) data were collected according to standardized Brain Resource International Database (BRID) procedure. Participants were seated in a comfortable chair in a dimly lit room 60 cm in front of a computer screen. Resting EEG was collected in two resting states: eyes open (EO) for two minutes where subjects were required to fixate on a red dot on the computer screen; and eyes closed (EC) for two minutes. Data were recorded from 26 scalp electrode sites according to the NuAmps International 10–10 electrode system, using a Quikcap with sintered Ag/AgCl electrodes. These data were recorded relative to the virtual ground, but referenced offline to linked mastoids with skin impedances less than 5 kOhms. Ocular (horizontal, vertical, and blink) artifacts were corrected offline according to the method of Gratton *et al.* [33]. EEGs were recorded at a 500 Hz sampling rate through a NuAmps amplifier. EEG data were screened visually for artefacts and epochs greater than 100 uV were automatically rejected.

2.2.3. *Event-related potentials: Working memory paradigm*

The working memory (WM) paradigm was an N-back task of sustained attention and low-load working memory updating. During EEG recording, participants were presented with a pseudorandomized series of white letters (B, C, D or G) on the computer screen for 200 ms each, separated by an interval of 2.5 s. Participants were asked to press buttons with the index finger of each hand in response to target

Table 1. Summary of the cognitive tests completed by the participants in this study.

Function	Task(s)	Description of Task	Variables Used in Analysis
Verbal declarative memory	Memory recall and learning	Subjects were presented with a list of 12 words 4 times, and after each presentation asked to recall verbally as many words possible. Distractor lists were then also presented. After a 25 min delay, subjects were asked to recall the original list, followed by a Memory Recognition test. Subjects were required to answer "yes" or "no" to a list of words that included the 12 original words and 12 new distractors.	• Immediate recall: Total number of words recalled trials 1–4 • Delayed memory recall • Memory recognition accuracy • Memory recognition rejection accuracy
Working memory, sustained attention, information processing speed	Sustained attention/ Working Memory (WM) Digit span	This encompasses the behavioral data for the WM task described in Sec. 2.2.3. Subjects viewed a series of single digits which they were required to enter onto a numberpad in the same order (either forwards or backwards). The number of digits in the series gradually increased from 3–9.	• Reaction time to targets • Number of commissions/omissions • Total score from correct trials in forwards digit span • Total score from correct trials in backwards digit span
	Span of visual memory	9 squares randomly distributed on the screen, would light up in order. The subject was required to follow the same sequence in order by pressing the squares on the touchscreen.	• Span of visual memory total number of correct trials
	Switching of attention	Similar to the Trails A and B task. Part 1 involved connecting a spatial arrangement of numbers in ascending order (1-26). Part 2 involved connecting a spatial arrangement of alphanumeric sequence (A-L and 1-13) in ascending but alternating order.	• Total duration to complete part 2

Table 1. (*Continued*)

Function	Task(s)	Description of Task	Variables Used in Analysis
Executive function	Verbal interference	Similar to the Stroop task. Subjects were presented with incongruent color-word combinations. Subjects were first required to name the word and not the color (visual interference) across a number of trials. Subjects are then required to name the color and not the word (verbal interference) across a number of trials.	• Visual interference total score correct • Verbal interference total score correct
Verbal processing	Word generation	Subjects were asked to generate as many words as possible beginning with the letters F, then A, then S (phonological fluency). Additionally, subjects were asked to name as many animals as possible (categorical or semantic fluency).	• Average number of words generated for letters F, A, S • Number of animals generated
	Spot-the-word	A measure of premorbid IQ. Real word and nonsense words were presented simultaneously, and subjects were required to determine which words were real.	• Spot the word total number of correct trials
Sensori-motor	Motor tapping	Subjects were required to tap a circle with their index finger as many times as possible within 30s. This was repeated for each hand.	• Average pause between taps for left hand • Average pause between taps for right hand
	Choice reaction time	Four black circles were presented on the screen, one of which would light up in green in turn. The subject was asked to move their finger from a central spot to the green circle as fast as possible.	• Average reaction time across trials

stimuli: defined as whenever the same letter appeared twice in a row. Speed and accuracy of response were equally stressed in the task instructions. There were 125 stimuli presented in total, with 85 non-target letters and 20 target letters. There were also 20 distractor stimuli (black and white 1×1 cm checkerboards) randomly interleaved with the letter stimuli that the subjects were instructed to ignore. As well as ERP components, psychometric measures were also collected including reaction time to targets and number of commissions/omissions that were included in the battery of cognitive measures. In this study, we were interested in the ERPs to background (non-target) stimuli, as this aspect has been shown to best capture the working memory updating process [19].

2.3. *Data analysis*

2.3.1. *Cognitive measures*

Data were screened for general artefacts, and outliers were defined as greater than 4 standard deviations from the mean. This accounted for only an extremely small portion of the normative data only (less than 0.01%), and as such, were removed. Missing data were not replaced.

Data for each variable were plotted in scatterplots against age, separately for each group.

2.3.2. *EEG*

Average power spectra were computed for the eyes open and eyes closed paradigms. The two minutes of EEG in each paradigm were first divided into adjacent intervals of four seconds. Power spectral analysis was performed on each four-second interval by applying a Welch window to the data, followed by a Fast Fourier Transform (FFT). The resulting power spectra were then averaged for each electrode position in each resting state over slow-wave frequency bands: delta (1.5–3.5 Hz) and theta (4–7.5 Hz); and fast-wave frequency bands: alpha (8–13 Hz) and beta (14.5–30 Hz). These data were then log transformed to attain normal distribution, and outliers were removed from power bands, and alpha peak amplitude/frequency, based on the interquartile method in order to systematically remove artefact data. Again, missing data were not replaced. In addition, the ratio of theta power to alpha power (representative of slow-wave to fast-wave ratio) was calculated.

To condense analyses, averages for the four power bands, theta/alpha ratio, alpha peak frequency and amplitude, were computed for four key brain regions collapsing across the following sites: frontal (Fp1, Fp2, F7, F3, Fz, F4, F8), central (FC3, FCz, FC4, C3, Cz, C4, CP3, CPz, CP4), temporal (T3, T4, T5, T6), and parietal-occipital regions (P3, Pz, P4, O1, Oz, O2). We were not interested in lateralized effects in the current study, but it will be a focus of future studies. Finally, scatterplots charted the EEG variables for each region of interest against age, for healthy normals, SMC, MCI and AD groups.

2.3.3. *Working memory ERP components to non-target stimuli*

Epochs were rejected if the signal at three or more sites exceeded 100 uV for that particular epoch. EEG data were filtered with a low-pass Tukey (cosine taper) filter that attenuated frequencies above 25 Hz. Data were baselined according to a 300 ms pre-stimulus time window. Peak amplitude and latency measures were determined at the focal sites of interest, FCz and CPz, as the sites of the maximal activation for background stimuli in this task [19]. Visual screening of the data identified four key ERP components: the N100, P150, N300 and P450 (WM P300). These ERP components were scored as the maxima within designated time windows by an automated scoring method, and were validated by manual scoring. The key components of interest in this study were the N300 and P450, reflecting memory retrieval and contextual updating processes, respectively [19, 26]. Scoring windows were shifted across the age span due to different morphology of the ERP waveform across age. Broadly, the time windows were: N300 (200–400 ms), P450 (300–540 ms). No outliers were identified and missing data were not replaced. Scatterplots were created which plotted the amplitude and latency scores for ERP components against age for each group.

2.3.4. *Calculation of the cross-sectional estimate of the "rate of decline"*

To quantify the "rate of decline" across the four groups examined, z-scores were first calculated for all subjects based on the mean of subjects aged between 48–52 years. This age group included only healthy controls and represented a continuation of the general decline across cognitive measures typically observed from around the age of 25–35 years [20]. In this way, a subject's score on each cognitive and brain measure was standardized according to this central point (see Fig. 1 below).

The cross-sectional estimate of the "rate of decline" was subsequently calculated and defined as the slope of the distribution of scores across age, separately for each of the four groups of interest. Linear regression was used to calculate the rates of decline specifically for all variables of interest, with age as the major predictor and the dependent variable being the z-score for each variable, as calculated above. These regressions were conducted for subjects above the age of 50 only (all clinical subjects and $n = 208$ normal subjects). "Rates of decline" were quantified by the unstandardized beta coefficients obtained through linear regression analyses, which defined the slope of the distribution of the subjects within the group, across age (see Fig. 1). These values represented the expected change in performance (in standard deviations) per year. In order to increase the interpretability of the calculated rates, they were multiplied by 10 to represent the change (in standard deviations) expected over 10 years for each group.

2.3.5. *Correlation analysis*

Additionally, we were interested in the association of memory decline and measures of brain function for each of the four groups examined. Partial correlations were

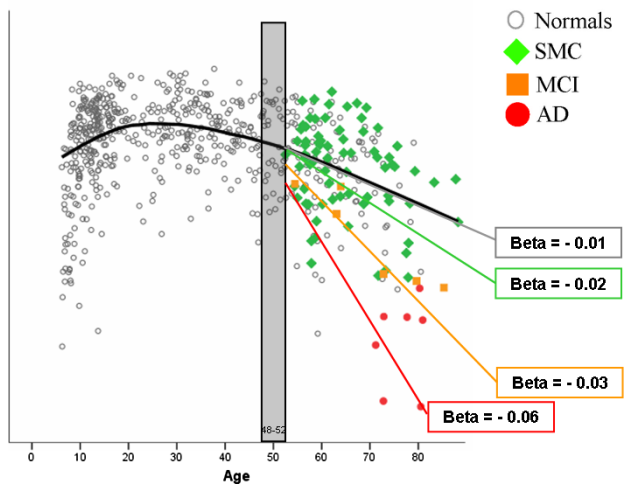


Fig. 1. Illustration of the calculation of the cross-sectional estimate of the "rate of decline". The data presented is a fictional dataset. The gray bar represents the "starting point" (age 48–52 years) against which change for each variable was measured. Scores for each group (Normals, SMC, MCI, AD) are plotted against subject's age on the x-axis. The "rate of decline" was determined from the slope of change (unstandardized beta coefficients) calculated via linear regression, with age as the predictor variable represented by beta values. As this example shows, the rate of decline differs across groups (decline in standard deviations each year), with AD subjects representing the biggest change relative to the 48–52 years starting point. In this study, better values were multiplied by 10 to indicate the rate of decline in SD's every 10 years.

performed while controlling for age, between all EEG and ERP measures and a measure of immediate memory (memory recall total score from trials 1–4). Correlations were conducted separately for each group including subjects over the age of 50. A threshold of significance was adopted at $p < 0.05$. Due to missing data across subjects, the numbers included in the analysis were: 108 normals, 73 SMC subjects, 6 MCI subjects and 7 AD subjects. It is noted that interpretation of the correlation data will take into account the low subject numbers in MCI/AD groups, and focus on consistent patterns of correlations with high correlation coefficients.

3. Results

3.1. *Cognitive measures*

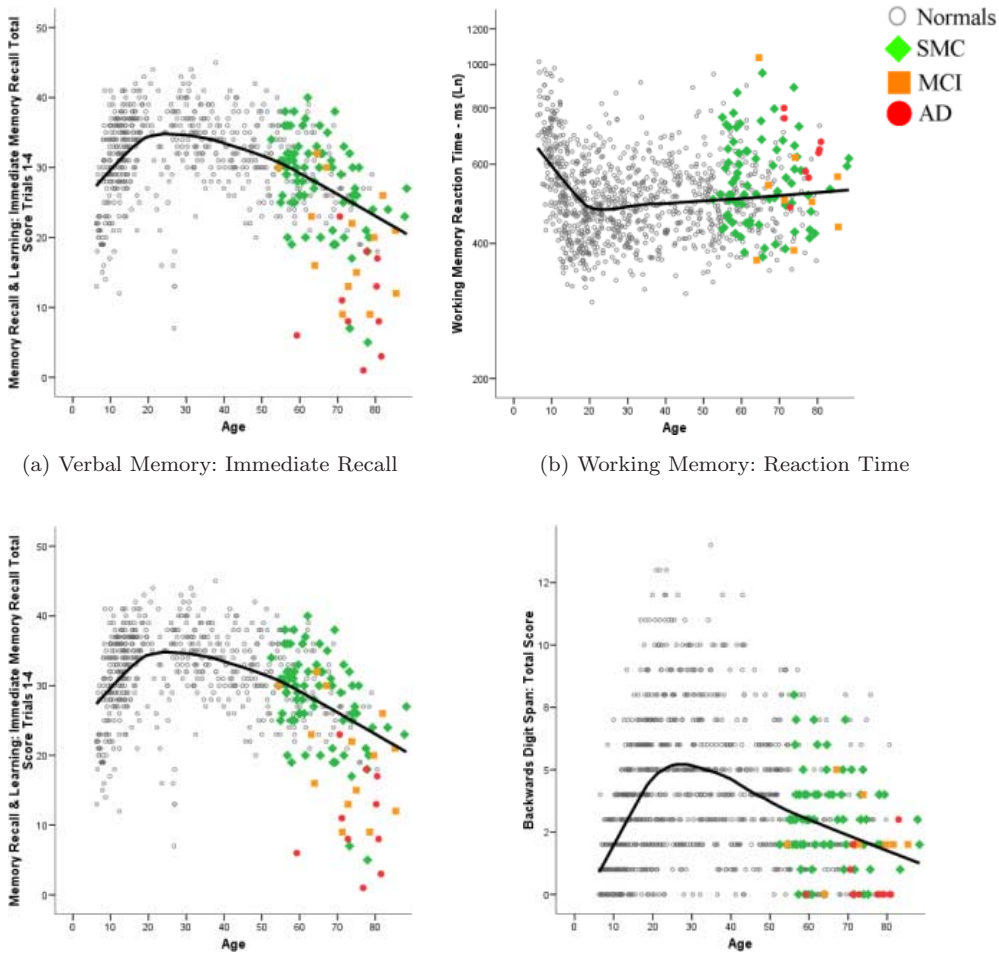
Table 2 presents the cross-sectional estimate of the "rates of decline" for cognitive variables (see Table 1) across the normal, SMC, MCI and AD cohorts in this study. Figure 2 presents scatterplots of these data for each group, plotted relative to age. In these scatterplots, the change in performance observed across healthy aging is represented by the fitted black line. While it is evident that cognitive functioning deteriorates cross-sectionally as part of healthy aging (corroborating with supporting evidence from the literature [20]), the cognitive decline associated with AD was excessive across all measures (Fig. 2). The cross-sectional estimates of the

Table 2. Cross-sectional "rates of decline" represented by expected increase (positive numbers) or decrease (negative numbers) in standard deviations every 10 years for cognitive measures in each group.

			Rate of Decline (No. SD's Every 10 Years)			
Function	Task	Variable	Normals	SMC	MCI	AD
Verbal memory	Memory recall and learning	Delayed verbal memory recall	−0.08	−0.08	−0.24	−0.36
		Memory recognition accuracy	−0.09	−0.1	−0.24	−0.4
		Memory recognition rejection accuracy	−0.04	−0.02	−0.39	−0.58
		Immediate memory recall: Total recall trials	−0.08	−0.11	−0.29	−0.48
Working memory and sustained attention	Sustained attention/ Working memory	WM response time	0.05	0.16	0.05	0.15
		WM total errors	−0.01	0.01	0.01	0.12
	Digit span	Forwards digit span total score	−0.03	−0.1	−0.14	−0.25
		Reverse digit span total score	−0.07	−0.08	−0.13	−0.24
	Span of visual memory	Span of visual memory total score	−0.05	−0.09	−0.27	−0.32
	Switching of attention	Switching of attention duration (part 2)	0.18	0.22	0.31	0.45
Executive function	Verbal interference	Visual Interference Score	−0.1	−0.19	−0.17	−0.4
		Verbal Interference Score	−0.14	−0.17	−0.25	−0.28
Verbal processing	Word generation	Letter: FAS (Phonetic) total score	−0.02	n/a	−0.14	−0.24
		Letter: Animal (Semantic) total score	−0.07	n/a	−0.14	−0.34
	Spot the word	Total score	0.03	n/a	−0.14	−0.43
Sensori-Motor	Tapping task	Average pause between left hand taps	−0.02	−0.01	0.04	−0.02
		Average pause between right hand taps	0.02	0.04	0.09	0.11
	Choice reaction time	Choice reaction time	0.06	0.11	0.31	0.36

"rates of decline" support this observation (Table 2). For instance, the AD subjects showed evidence of an amplified deterioration in performance on a measure of immediate verbal memory recall [Fig. 2(a)]. The rate of decline indicated that the AD group showed decreased memory performance by 0.48 SD's every 10 years (cross-sectionally).

MCI subjects showed somewhat similar patterns of decline in memory function but at a slower rate across age than the AD group (0.29 SD's per 10 years). By



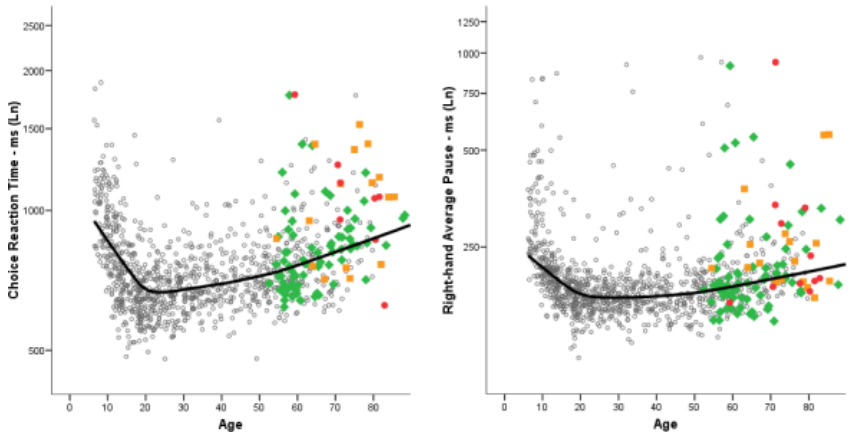
(a) Verbal Memory: Immediate Recall

(b) Working Memory: Reaction Time

(c) Executive Function: Verbal Interference

(d) Working Memory: Digit Span (Backwards)

Fig. 2. Scatterplots show the cognitive performance of individuals in the normal (gray circles), SMC (green diamonds), MCI (orange squares), AD (red circles) groups on cognitive tests plotted against age (years). The black line represents the line of best fit for the normal cohort (gray circles). Measures shown are: (a) Performance on an immediate verbal memory recall task; (b) Reaction time to target stimuli in working memory continuous performance task; (c) Total score achieved on the verbal interference task; (d) Total score achieved on the reverse digit span task; (e) Reaction time to target stimuli in the choice reaction time task; (f) Average pause for right-hand taps during the tapping task.



(e) Sensori-Motor: Choice Reaction Time (f) Motor: Tapping

Fig. 2. (*Continued*)

contrast, healthy subjects were found to decline at a rate of 0.08 standard deviations per 10 years (after the age of 50), and SMC subjects showed a similar pattern (0.11 standard deviations per 10 years).

Similar patterns were observed across other measures encompassing prominent cognitive domains. Advanced decline for the AD group was particularly marked for measures of verbal memory [Fig. 2(a)], working memory [Fig. 2(b)], verbal processing (Table 2), digit span [Fig. 2(d)] and switching of attention. The MCI group showed comparable patterns of decline to AD subjects across age on measures of visual memory, executive function [verbal interference: Fig. 2(c)], and choice reaction time [Fig. 2(e)], suggesting that cognitive decline is evident preclinically in this cohort. Further, decline in a similar direction but at a reduced rate (Table 2) was also evident for performance on verbal memory, verbal processing and digit span tasks. Note that in the digit span (forwards and backwards) tasks, scores of zero most likely reflect reduced processing speed since a limited time is provided in which to respond (5 seconds). The AD group, showed a significant number of zero scores on this task, suggesting reduced processing speed, which corroborates with supporting evidence from the other cognitive measures.

Interestingly, while choice reaction time (a measure of sensori-motor function) was sensitive to distinguishing between AD and other groups, the AD cohort did not show particular decline on the motor tapping task relative to normals or other groups [see Fig. 2(f)].

In summary, while SMC subjects followed similar trends in cognitive decline to healthy subjects from the age of 50 years, MCI and AD patients in particular, showed advanced deviations away from normal aging trends. These findings indicate that cognitive measures, including those of memory, executive function, processing speed and verbal ability, are sensitive to the preclinical decline in cognition associated with MCI. Further degradation in function across these groups reflects a possible

quantitative decrease in performance that is likely to have been evident preclinically in these subjects.

3.2. *EEG measures*

Table 3 presents the cross-sectional estimates of the calculated rates of decline across measures of EEG, including slow-wave power (delta and theta), fast-wave power (alpha and beta), theta to alpha power ratio, alpha peak frequency and amplitude. All these measures were investigated in eyes open (EO) and eyes closed resting conditions (EC). Figure 3 presents scatterplots of these data for each group, plotted relative to age.

The results suggest that AD subjects were characterized by acute deviations from normal aging expectations over measures of resting EEG, relative to the trends observed for other groups. There was a clear pattern where slow-wave EEG was increased and fast-wave EEG decreased in AD subjects. Theta power was

Table 3. Cross-sectional estimates of the "rates of decline" indicate the expected increase (positive numbers) or decrease (negative numbers) in standard deviations every 10 years for EEG measures in each group.

			Rate of Decline (No. SD's Every 10 Years)			
Resting State	EEG Band	Region	Normals	SMC	MCI	AD
EO	Delta Power	Frontal	−0.03	−0.04	−0.07	0.07
		Central	−0.07	−0.13	−0.05	−0.04
		Temporal	−0.06	−0.14	−0.15	0.03
		Parietal-Occipital	−0.07	−0.16	−0.1	−0.04
EC	Delta Power	Frontal	−0.04	−0.04	−0.02	0.07
		Central	−0.06	−0.1	−0.06	−0.03
		Temporal	−0.05	−0.11	−0.09	0.02
		Parietal-Occipital	−0.06	−0.14	−0.04	−0.04
EO	Theta Power	Frontal	−0.06	−0.04	0.09	0.17
		Central	−0.07	−0.09	0.07	0.09
		Temporal	−0.07	−0.12	−0.03	0.14
		Parietal-Occipital	−0.06	−0.11	−0.02	0.09
EC	Theta Power	Frontal	−0.05	0	0.06	0.11
		Central	−0.06	−0.04	0.01	0.05
		Temporal	−0.06	−0.06	−0.04	0.07
		Parietal-Occipital	−0.07	−0.08	−0.02	0.03
EO	Alpha Powers	Frontal	−0.03	0.02	0.06	0.02
		Central	−0.04	0	0.04	0
		Temporal	−0.04	−0.02	−0.02	0
		Parietal-Occipital	−0.04	−0.02	−0.01	−0.01
EC	Alpha Power	Frontal	−0.05	0.02	0.01	−0.1
		Central	−0.06	−0.01	−0.01	−0.11
		Temporal	−0.05	−0.01	−0.04	0.11
		Parietal-Occipital	−0.06	−0.03	−0.04	−0.12

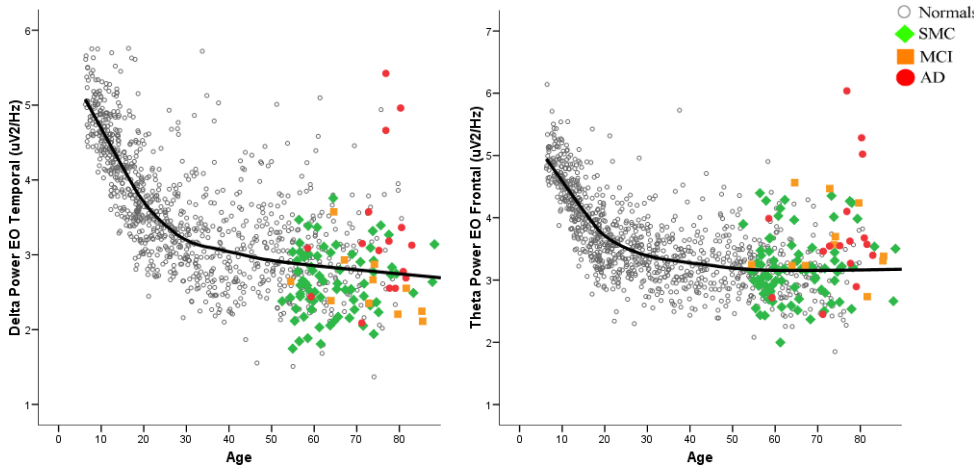
Table 3. (*Continued*)

Resting State	EEG Band	Region	Rate of Decline (No. SD's Every 10 Years)			
			Normals	SMC	MCI	AD
EO	Alpha Peak Amplitude	Frontal	−0.01	0.05	0.08	0.07
		Central	−0.03	0	0.03	0.1
		Temporal	−0.03	−0.02	0	0.09
		Parietal-Occipital	−0.03	−0.04	0	0.08
EC	Alpha Peak Amplitude	Frontal	−0.03	0.09	−0.07	−0.06
		Central	−0.06	−0.02	−0.08	−0.07
		Temporal	−0.06	−0.01	−0.1	−0.07
		Parietal-Occipital	−0.06	−0.05	−0.1	−0.08
EO	Alpha Peak Frequency	Frontal	0	−0.01	−0.08	−0.06
		Central	0	0	−0.07	−0.06
		Temporal	−0.01	−0.03	−0.11	−0.09
		Parietal-Occipital	−0.01	−0.01	−0.1	−0.09
EC	Alpha Peak Frequency	Frontal	−0.02	−0.03	0.03	−0.17
		Central	−0.01	−0.02	0.06	−0.11
		Temporal	−0.04	−0.05	0.01	−0.2
		Parietal-Occipital	−0.04	−0.04	0.01	−0.16
EO	Beta Power	Frontal	−0.04	−0.05	−0.01	0.02
		Central	−0.03	−0.02	0.03	−0.03
		Temporal	−0.05	−0.1	−0.04	−0.03
		Parietal-Occipital	−0.04	−0.05	−0.06	−0.09
EC	Beta Power	Frontal	−0.04	0.01	0.04	−0.03
		Central	−0.04	0	0.01	−0.11
		Temporal	−0.06	−0.06	−0.05	−0.07
		Parietal-Occipital	−0.06	−0.05	−0.06	−0.16
EO	Theta/Alpha Ratio	Frontal	−0.01	−0.06	−0.01	0.12
		Central	−0.02	−0.1	−0.03	0.1
		Temporal	−0.04	−0.12	−0.04	0.18
		Parietal-Occipital	−0.01	−0.1	−0.02	0.13
EC	Theta/Alpha Ratio	Frontal	0.02	−0.03	0.02	0.25
		Central	0	−0.08	−0.01	0.22
		Temporal	0	−0.08	−0.01	0.3
		Parietal-Occipital	0	−0.05	0.01	0.23

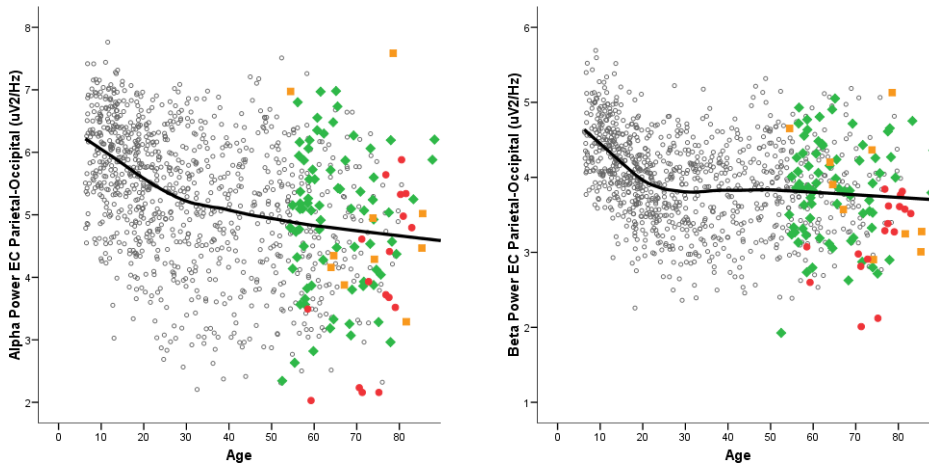
particularly increased frontally in the EO condition [Fig. 3(b)], whereas, alpha and beta power was greatly decreased [alpha during EC globally: Fig. 3(c); beta during EC especially posteriorally: Fig. 3(d)]. This imbalance between slow-and fast-wave EEG is captured by the theta/alpha power ratio [Fig. 3(f)]: distinguishable increases in this ratio were observed in the AD group particularly posteriorally in the EO condition (at a rate of 0.18 SD's per 10 years at temporal sites), and globally in the EC condition (e.g., 0.25 SD's per 10 years frontally). Furthermore, other measures of alpha also revealed specific decreases for the AD group (see Table 3) that were not evident in other groups. Alpha peak amplitude was decreased globally in the EC condition (although increases in the EO condition relative to normal

aging expectations), and alpha peak frequency was decreased especially in the EC condition [Fig. 3(e)], across age for AD subjects.

Similar to AD, MCI subjects showed patterns of increased theta power (fronto-centrally), indicating that some patterns of resting brain activity linked to AD may be able to be observed preclinically. By contrast, measures of slow-wave EEG power did not show patterns distinct from that expected via normal aging (with the

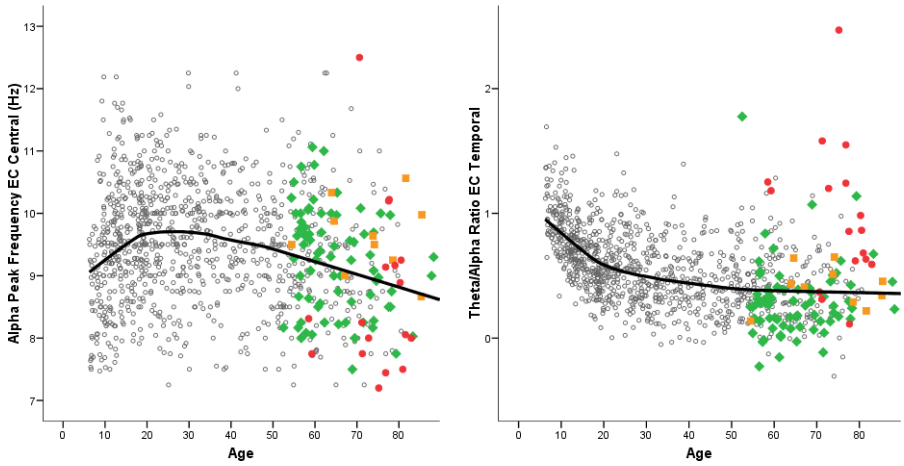


(a) Delta Power (b) Theta Power



(c) Alpha Power (d) Beta Power

Fig. 3. Scatterplots demonstrating decline on measures of resting EEG across individuals in the normal (gray circles), SMC (green diamonds), MCI (orange squares), AD (red circles) groups on measures of resting EEG (eyes open: EO and eyes closed: EC) plotted against age (years). The black line represents the line of best fit for the normal cohort (gray circles). Measures shown are: (a) Delta power in EO condition averaged over temporal sites; (b) Theta power during EO condition averaged over frontal sites; (c) Alpha power in EC condition averaged over parietal-occipital sites; (d) Beta power in EC condition averaged over parietal-occipital sites; (e) Alpha peak frequency in EC condition averaged over central sites; (f) Ratio of theta to alpha power in EO condition averaged over temporal sites.



(e) Alpha Peak Frequency (f) Theta/Alpha Power Ratio

Fig. 3. (*Continued*)

exception of trends toward increased alpha power during EO resting state fronto-centrally). Indeed, measures of theta/alpha ratio in the MCI group did not show the same increases that were evident in AD subjects [Fig. 3(f)]. There were however, comparable findings concerning the alpha peak: MCI patients showed a trend toward increased alpha peak amplitude during EO (fronto-centrally), and decreased alpha peak amplitude during the EC, similar to AD subjects (Table 3).

Moreover, MCI subjects also showed specific differences relative to normal aging expectations. While measures of delta power in the resting state decreased across age in healthy subjects (e.g., at a rate of 0.06 SD's per 10 years at temporal sites in the EO condition) and AD subjects showed only mild increases in delta power over fronto-temporal regions (at a rate of 0.03 SD's per 10 years at temporal sites in the EO condition), MCI and SMC groups showed exaggerated decreases in delta power across age (0.14 and 0.15 SD's respectively per 10 years at temporal sites in the EO condition). Contrasting a decrease in resting delta power for normal, SMC and MCI (which also showed increases in slow-wave activity within theta) groups, versus fronto-temporal increases in delta power in AD subjects (combined with exacerbated increases in theta power), may underpin a key biological difference between relatively healthy aging or preclinical brains (SMC/MCI) versus brains suffering from pathological aging (AD).

SMC subjects showed patterns of EEG changes across age generally resembling those of normal healthy aging, including decreases in delta (although the decline was amplified particularly posteriorally as remarked above), theta (again, especially posteriorally), and similar patterns in alpha/beta power. Alpha peak amplitude was increased frontally, in both EO (similar to MCI and AD groups) and EC conditions. Again, changes in alpha peak frequency across age in SMC subjects, was not distinct from changes observed in the normal group.

3.3. *Working memory ERPs*

Table 4 presents the cross-sectional estimates of the rate of decline calculated for the working memory ERP components — N300 and P450. In summary, the AD group showed specific decreases in the P450 amplitude at both recording sites of interest, relative to the expectations of normal aging, and to the changes across age observed in both MCI and SMC groups [Fig. 4(b)]. While the latency of the P450 component was also delayed in the AD group, similar delays were also observed in the MCI and normal groups across age (see Table 4).

By contrast, the MCI group showed specific reductions in the N300 component amplitude, particularly at the centro-parietal site (CPz), whereas SMC and AD groups showed mild increases in N300 amplitude across age [Fig. 4(a)]. Note that increased amplitude (in the positive direction) must be interpreted as an actual *decrease* in the amplitude of the negative ERP component. This reduction was supported by N300 delays in the MCI group, also evident in the AD group (but at a reduced rate of decline). Slowing of ERP components reflecting the operation of controlled memory processes, suggests slowed cognitive processes. The dissociation concerning changes in the amplitude of the N300/P450 components across age between MCI and AD groups respectively, may reflect core underlying differences distinguishing AD from preclinical phases of dementia.

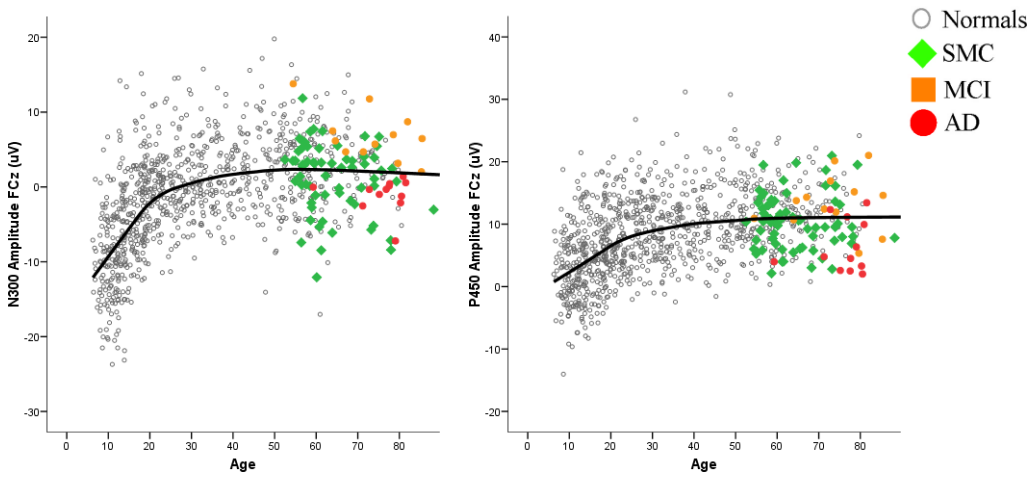
3.4. *Correlations*

Correlations between EEG/ERP measures and an index of memory performance (total memory recall across trials 1–4 reflecting immediate recall), were conducted separately for each group. These correlations are presented in Table 5.

Specific correlation patterns were evident for each group, reflecting the specific deviations from normal aging expectations related above. In AD subjects, memory

Table 4. Cross-sectional estimates of the "rates of decline" indicate the expected increase (positive numbers) or decrease (negative numbers) in standard deviations every 10 years for working memory ERP measures in each group. Amplitude and latency variables are both presented.

Working Memory Background ERPs			Rate of Decline (No. SD's Every 10 Years)			
ERP Component	Amplitude/ Latency	Site	Normals	SMC	MCI	AD
N300	Amplitude	FCz	0	−0.03	0.01	−0.08
	Amplitude	CPz	0	−0.03	0.09	−0.06
	Latency	FCz	0.03	−0.05	0.14	0.05
	Latency	CPz	0.03	−0.04	0.13	0.05
P450	Amplitude	FCz	−0.01	−0.04	0.03	−0.12
	Amplitude	CPz	−0.01	−0.03	0.02	−0.12
	Latency	FCz	0.07	−0.02	0.09	0.08
	Latency	CPz	0.06	−0.03	0.07	0.06



(a) N300 Amplitude (b) P450 Amplitude

Fig. 4. Scatterplots demonstrating decline on measures of working memory ERP activity across individuals in the normal (gray circles), SMC (green diamonds), MCI (orange squares), AD (red circles) groups plotted against age (years). The black line represents the line of best fit for the normal cohort (gray circles). Measures shown are: (a) N300 component amplitude recorded at FCz; (b) P450 component amplitude recorded at FCz.

decline was specifically associated with increases in theta power over the parietal-occipital region (EC), and with theta/alpha ratio globally (EO/EC). Additionally, memory performance was positively correlated with alpha peak frequency in the EC condition for the AD group only. These findings suggest that advanced deterioration in memory function observed in AD subjects across age is related to changes in brain function reflecting cortical hypoarousal and neuropathology.

By contrast, positive correlations between delta power (across central, temporal, parietal regions in the EO condition) and immediate memory recall were observed in the MCI group only, reflecting the exaggerated decrements in delta power shown by the MCI/SMC groups across age. These results suggest that delta power could be a correlate of memory decline in MCI, and therefore could be considered a sensitive marker for differentiating between those within preclinical phases of dementia versus individuals in more advanced phases of dementia decline.

Similar to the AD subjects, positive correlations between memory and alpha peak frequency (EO), but negative correlations with theta at fronto-central regions (EO) were observed for SMC subjects.

Healthy subjects also showed positive correlations between memory and delta power at central-parietal sites during the EC condition, but also positive correlations between alpha peak amplitude at central-parietal regions in the EC condition.

Correlations with the N300 and P450 ERP components did not reveal significant effects for MCI/AD subjects respectively, although trends were evident that may be examined in larger subject groups. Healthy subjects showed a positive correlation

Table 5. Correlations between memory performance and EEG/ERP measures for normal, SMC, MCI and AD subjects. Pearson's r-values are presented, and strength of correlation is marked in color: yellow ($p < 0.05$), orange ($p < 0.01$), red ($p < 0.001$).

Resting State	EEG Band	Region	Correlations			
			Normals	SMC	MCI	AD
EO	Delta	Central			$r = 0.767$	
		Temporal			$r = 0.751$	
		Parietal-Occipital			$r = 0.758$	
EC	Delta	Central	$r = 0.197$			
		Parietal-Occipital	$r = 0.235$			
EO	Theta	Frontal		$r = -0.228$		
		Central		$r = -0.209$		
EC	Theta	Parietal-Occipital				$r = -0.627$
EC	Alpha Peak Amplitude	Central	$r = 0.242$			
		Parietal-Occipital	$r = 0.252$			
EO	Alpha Peak Freq	Frontal		$r = 0.269$		
		Central		$r = 0.298$		
		Temporal		$r = 0.283$		
		Parietal-Occipital		$r = 0.256$		
EC	Alpha Peak Freq	Frontal				$r = 0.779$
		Central				$r = 0.901$
		Temporal				$r = 0.671$
		Parietal-Occipital				$r = 0.82$
EO	Theta:Alpha Ratio	Frontal				$r = -0.719$
		Central				$r = -0.663$
		Temporal		$r = -0.193$		$r = -0.644$
		Parietal-Occipital				$r = -0.724$
EC	Theta:Alpha Ratio	Frontal				$r = -0.64$
		Central				$r = -0.635$
		Temporal				$r = -0.645$
		Parietal-Occipital				$r = -0.678$

Working Memory Background ERPs			Correlations			
ERP	Amp/Lat	Site	Normals	SMC	MCI	AD
N300	Amplitude	FCz		$r = 0.251$		
	Latency	FCz	$r = 0.247$			
		CPz	$r = 0.227$			
P450	Amplitude	FCz	$r = 0.167$	$r = 0.223$		
		CPz		$r = 0.207$		
	Latency	FCz		$r = 0.233$		
		CPz		$r = 0.231$		

Significance: $p < 0.05$, $p < 0.01$, $p < 0.001$

between N300 latency at both sites, and the P450 amplitude at FCz, suggesting that as memory increases, the N300 is delayed and P450 increases. This supports the premise that reductions in P450 component reflecting context updating processes could be integral to the working memory and cognitive deficits observed in the AD subjects. Additionally, SMC subjects showed positive correlations between memory performance and the N300 (at FCz) and P450 amplitude (at both sites), suggesting that N300 reductions are associated with increased memory performance in this group only. Positive correlations were also observed between P450 latency and memory performance for the SMC group.

4. Discussion

This study revealed that an increased functional decline was observed in Alzheimer's disease, relative to the decline expected through the processes of normal aging. This was examined by charting the change in key cognitive, EEG and ERP markers cross-sectionally across age. As predicted, SMC and MCI groups were found to represent intermediate stages between the level of deterioration observed in healthy individuals and AD patients, consistent with the prodromal nature of these conditions. The MCI group in particular, was distinguished by its own unique set of EEG and ERP markers. Significant correlations indicated that deficits in memory function across groups showed distinct interactions with psychophysiological variables, suggesting that there are at least partially distinct processes contributing to the decline associated with normal aging relative to preclinical phases of dementia and AD. While it is likely that there are several intersecting contributing factors that predict decline in cognitive ability in older age [17], the data presented here supports a continuum model to represent the relationship between the functional decline in normal aging and AD [27, 76]. These patterns will need to be further examined in larger numbers and within a longitudinal study in order to better understand the decline in individuals as they progress from preclinical phases to AD.

Although a cross-sectional study, quantification of the relative deterioration across age was achieved via the calculation of the estimate of the "rate of decline" across age for each group. This method represented a descriptive statistical technique to quantify rates of change. These findings support the argument that there is a continuum of deterioration in cognitive function from normal aging, through preclinical stages to dementia [27, 76]. Cognitive variables were effective for distinguishing AD as showing advanced decline across age, relative to all other groups. Patterns of performance revealed a *quantitative* decline from normal through to preclinical and AD groups over cognitive variables reflecting memory, language, attention and executive function. SMC deficits generally resembled the deterioration in cognitive ability that would be expected through normal aging, consistent with the non-pathological status of this group. By contrast, the differences in the rates of decline between groups measured by psychophysiological (EEG/ERP) variables were more *qualitative* in nature. The AD group showed heightened slow-wave activity over age

(particularly within the theta band), counteracted by decreased fast-wave activity (both alpha and beta power), reflected most prominently in the theta/alpha power ratios. Together with decreases in alpha peak frequency, the theta/alpha power ratio was directly associated with decline in memory performance in a subset of the AD group. While the MCI group showed a similar trend toward increased theta and decreased fast-wave activity over age, the group also showed patterns of *decreased* delta power (also observed in SMC subjects), compared to normal aging expectations. This discrepancy may be an important marker of greater deterioration in preclinical phases, and suggests a shift toward the theta band in the resting state. Importantly, decreased delta power was uniquely related to decline in memory ability in a subset of MCI subjects. Consistent with this dissociation between MCI and AD, working memory ERPs also revealed that AD subjects were characterized by distinct reductions in the working memory P450 component across age. In contrast, MCI subjects showed greater N300 component amplitude decreases across age. This dissociation may reflect a global deficit in contextual updating processes in AD subjects, as opposed to a more focal deterioration in memory retrieval processes in MCI subjects. This study provides important integrative evidence for quantifying the deterioration in cognitive and brain functioning associated with normal aging versus that observed in pathological aging. It is proposed that these significant markers could represent critical stages in the transition between preclinical dementia to Alzheimer's disease, and provides a platform for future studies.

4.1. *Cognitive measures*

Measures of short-term declarative verbal memory in the current study were found to be a prominent marker in modeling the degraded decline in ability from normal aging, through prodromal groups to AD over age (Fig. 2). This increased decline in the AD group is reflected in the cross-sectional estimates of the "rate of decline" (Table 2). This corroborates with existing evidence suggesting that verbal memory deterioration (episodic, semantic) is specifically marked in dementia [66], and elements of which may represent key markers for distinguishing normals from AD patients [48]. However, it is important to note that memory ability also represents a key aspect of the initial clinical assessment criteria for determining an AD diagnosis [56, 73]. This limitation when considering only cognitive data supports the need for an integrative approach incorporating both cognitive and direct objective measures of brain function.

A similar profile of cognitive decline was also revealed in domains of cognition encompassing executive function, verbal processing, attention, working memory, speed of processing and sensori-motor function. In all measures (with the exception of the motor tapping task), AD subjects showed enhanced rates of decline relative to all groups, where there appeared to be a quantitative shift in decline observed between normal aging, SMC, MCI and AD cohorts across age. MCI subjects also showed trends toward advanced decline but at a reduced rate relative to AD across

age over these measures, (see Table 2), especially involving span of visual memory, choice reaction time and executive function (verbal interference) measures. This data indicates that the MCI (and to a lesser extent, SMC) conditions may represent an intermediate state of cognitive impairment, which is supported by other findings in the literature [37]. The separation of amnestic and non-amnestic MCI over cognitive measures is expected [60], and will be examined in future studies.

We note that not all cognitive domains known to be specifically impaired in AD were assessed by the computerized battery of tests our subjects completed. Further examination with additional data measuring confrontation naming, apraxia, visuospatial construction, for instance, will be required in order to further determine the pattern of loss in AD as it relates to the pattern of loss in normal aging. It is speculated that performance within these specific domains will show particular deficits in AD, and represent a distinction, rather than a continuum, from normal aging expectations. The value of the current approach is that *all* subjects (healthy and clinical cohorts) completed the same standardized testing battery, which taps into a wide spectrum of cognitive abilities [59].

These findings corroborate with literature outlining the effectiveness of the prediction to conversion from MCI to AD using neuropsychological measures [5, 14, 16, 39, 50, 51]. Yet, the consideration of only cognitive markers does not provide adequate levels of sensitivity [43], and it is argued that accurate predictions must rely on other measures of biological, physiological function and genetic information [5, 10, 55].

4.2. *EEG measures*

Measures of resting state EEG provide an index of the arousal of the brain and measure the brain's oscillatory activity, as a prelude to engagement in cognitive activity. AD patients in this study showed characteristic EEG patterns reported in the literature, relative to normals [4, 25, 47]. Firstly, AD patients revealed increased slow-wave EEG especially within the theta band over age [fronto-temporally — Fig. 3(b)] although there was evidence of mild increases across age in delta power over frontal regions [Table 3, Fig. 3(a)]. By contrast, alpha power in particular [Fig. 3(c)], and to a lesser extent beta power [especially over parietal-occipital recording sites — Fig. 3(d)] were decreased over age. This observation of an increase in slow-wave (synchronization) and decrease in fast-wave EEG (desynchronization) is supported by the theta/alpha ratio measure in AD patients. This dissociation between theta and alpha in resting EEG is argued to reflect decreased performance abilities, and is a common neural correlate for a variety of neurological disorders [44], and likely to reflect the death of the connections between neurons underpinning AD [34]. Such a pattern may reflect general cortical under-arousal in the resting state of AD patients. Indeed, measures of theta/alpha power ratio negatively correlated with memory performance (immediate memory recall) in a subset of AD subjects, across all regions in both EO/EC resting conditions. Although in small numbers, these correlations were

high and consistent across both resting conditions and all brain regions. Memory ability has been used in clinical assessments as an indication of dementia severity, and the ratio of slow-wave to fast-wave EEG may provide an objective biological correlate of this severity, with age as a potential factor.

Other measures of alpha activity were also found to be particularly decreased in AD patients: alpha peak frequency and amplitude showed increased rates of decline relative to both normals and preclinical stages of dementia across age. In the EC condition, alpha peak frequency was found to positively correlate with memory performance, particularly over central sites (showing even stronger, consistent correlations), thus providing a corroborating marker with the theta/alpha ratio measure. Decreases in alpha peak frequency have been consistently associated with decreases in memory performance, even in normal subjects [18, 46]. These findings are likely to be related to an enhanced slowing of the EEG in aging subjects with concomitant pathology (AD), which appears to be associated with memory ability [45]. As such, measures of alpha peak frequency have been promoted as viable predictive markers of dementia-onset [44]. This is an issue to be further examined using phasic or task-related EEG measures.

MCI patients showed some similar patterns of resting-state EEG to those observed in the AD cohort. There was evidence of increased theta over age (although only fronto-centrally, and to a lesser degree). Fast-wave EEG power did not decrease any more than would be expected in normal aging [Table 3, Figs. 3(c)–3(d)], although alpha peak frequency was particularly diminished in the EO condition [Fig. 3(e)]. Delta power generally decreased across age in healthy individuals, but most significantly, was found to be especially decreased in both MCI and SMC groups [Table 3, Fig. 3(a)]. This contrast of a decrease in delta power but increase in theta power, both defined as slow-wave EEG, suggests a shift toward the theta frequency band in MCI subjects. This could reflect the operation of adaptive strategies in MCI subjects to compensate for preclinical neural changes prior to accelerated neuronal death associated with dementia. Theta activity has been linked to hippocampal oscillations in animal studies [44]. Specific emphasis on EEG resting activity in the theta band in MCI subjects could potentially reflect more focal disruption of the operation of the hippocampus, where reductions in volume have been observed preclinically [10], and may underpin isolated memory deficits. Correlations performed in the current study show that this decrease in delta power is specifically related to memory performance decline in a subset of MCI subjects. Again, although correlations were conducted with small numbers, correlations were high and consistent across brain regions. This is opposed to more general deficits evident in the AD group, likely to be underpinned by the spreading of neural degeneration into the greater temporal and frontal cortical regions for instance [15, 70] and reflected in the increased slow-wave to fast-wave resting EEG ratio for this group across age.

SMC represents a preclinical phase with patterns of decline across age reflecting normal changes, although delta power was also especially decreased (without the

concomitant increases in theta observed in MCI). Such patterns may also signify objective evidence of preclinical changes, prior to the progression toward MCI and AD. Indeed, alpha peak frequency was positively correlated with memory performance in both SMC and AD groups, in a pattern distinct from normal aging.

4.3. *ERP measures*

Complementary to resting EEG observations, working memory ERPs provide objective measures of the activity of the brain in the active state. There was a double dissociation observed between rates of decline observed in AD and MCI groups concerning the working memory P450 and N300 ERP components respectively.

AD subjects showed decreased P450 components at both recording sites of interest, as well as delayed latency, across age. Patterns for both preclinical groups over age closely matched those of the normal group for this component (Table 4). The P450 component is considered an index of context updating processes, vital in the efficient updating of working memory during this task [19]. Deficiencies in the context updating mechanism in AD have been previously reported, and have been found to reliably discriminate early AD patients from healthy older individuals [11]. Such deficits may arise due to accelerated problems in the usual phasic-driven dopaminergic projections from the midbrain the lateral prefrontal cortex in response to significant stimuli [11]. This may be a concomitant functional deficit due to advanced fronto-temporal cortical degeneration observed in AD [6, 9]. Other hypothesized neurotransmitter system abnormalities include loss of cholinergic function in the basal forebrain, which projects diffusely through to the cortex modulating phasic neural activity that generates the ERP (e.g., Ref. 3). General problems in updating, representing, interpreting and responding to new contextual information will follow if these systems are disrupted. While normal aging incurs such deterioration, dysfunction is advanced in AD, as indicated by the advanced amplitude decline in the working memory P450 marker in this group.

By contrast, the working memory N300 component was specifically decreased and delayed in MCI subjects, relative to normal, SMC and AD subjects. The N300 in the WM task has been argued to reflect the operation of controlled memory retrieval processes [26]. AD patients appear to display global and perfuse functional deficits incorporating wide-spread dysfunction across brain regions reflected in resting EEG and P450 reductions. By contrast MCI subjects, as a high-risk prelude to conversion to dementia, appear to show more focal deficits. Decreases in delta power (yet increases in theta power), coupled with decreases specifically in the N300 WM component, suggest the potential operation of compensatory mechanisms in an attempt to adapt to progressive neurological changes characteristic of preclinical phases, both cognitively and psychologically [63].

It is acknowledged that the MCI and AD datasets contain relatively smaller numbers than the normal and SMC cohort. All statistical analyses were conducted with

normal subject's aged over 50, where variability over groups were mostly comparable and examined via standard deviations, although there is growing evidence that intrasubject diversity increases with age [17]. In some cases however, particularly for measures of reaction time, and EEG power, the AD group showed greater variability amongst subjects. Given the cross-sectional nature of this study, the findings and conclusions will need to be tested both longitudinally and in larger datasets in order to substantiate evidence for predictive markers of dementia. Further consideration of early vs late onset AD which may have a contributing factor to dementia symptoms other than AD etiology [53], and severity of symptoms can be examined with larger subject groups. This would enable the examination of greater subtle variations in patterns of response (for example, non-linear changes), to account for heterogeneity in groups (early/late onset AD, range of severity of dementia) and potentially integrate with other markers identified as important, such as genetics, structural brain imaging and social cognition [32].

4.4. *Conclusions and integrative significance*

The patterns observed over cognitive and psychophysiological measures reflect a quantitative and qualitative shift respectively, between the advancing deterioration of function expected via the processes of normal aging, compared to preclinical subjective (SMC) and objective prodromal phases of dementia (MCI), and AD. Although a cross-sectional study, the calculation of the estimated "rates of decline" suggest that it is important to consider age as a factor when examining markers for AD onset. Our findings suggest that it is the combination of markers across cognitive and psychophysiological measures that enable the reliable assessment of the proposed continuity of decline observed as symptom severity advances from preclinical through to dementia groups. Key markers for AD changes over age were identified: advanced decline in performance across cognitive domains, increases in slow-wave to fast-wave ratio and decreases in alpha peak frequency in the resting state, which were associated with decreases in memory ability across age, coupled with specific decreases and delays in the working memory P450 ERP component. Normal aging has been explained by the popular frontal aging hypothesis, and which is commonly distinguished from the processes underpinning AD. However, the data presented here suggests that the increase rate of decline over age evident between normal aging and AD could be represented on a continuum, although the underlying neural mechanisms that contribute to such decline may be somewhat distinct, as suggested by specific correlations between brain and cognitive measures. For instance, it may be that exaggerated frontal lobe decline could explain decline in memory abilities in normal aging, whereas predominant deterioration observed bilaterally in the hippocampus may explain the decline in memory associated with AD [38]. Furthermore, it has been reported in longitudinal and meta-analysis studies that it is highly likely that there are multiple contributing factors to changes in cognition in normal aging including education, health, low activity, and the presence of

the APOE $\varepsilon 4$ allele [17]. Given that these factors are also likely to predict AD [10] further supports a continuum model of decline. The distinction of AD from normal aging decline is an important research question that requires further elucidation.

Current key biomarkers can only be reliably measured post-mortem [24], whereas EEG/ERP markers represent non-invasive objective measures of cortical arousal during rest and activity, respectively. Establishing a profile of symptoms for individuals that will enable precise tracking of disease progression over age, which may occur at different rates over age across symptoms, could advance dementia treatment toward a personalized medicine approach [29].

The MCI condition represents greater risk for development of Alzheimer's dementia [60], and thus, it is becoming increasingly important to establish reliable markers for *when* an individual may progress to MCI. This study points to 3 key markers that distinguish MCI from subjective preclinical phases, normal healthy aging and AD. These are: relatively increased rates of decline in measures of cognitive performance (memory, executive function, processing speed and visual memory) compared to healthy subjects; exaggerated decreases in delta power (which correlated with memory deficits), coupled with increases in theta power over age; and specific decreases in the working memory N300 amplitude over age (combined with delayed latencies for both N300 and P450 components).

The establishment of objective markers that signal distinct rates of decline across age for MCI relative to AD, could be vital indicators of the critical turning points in the transition between preclinical phases of disease and through to the onset of dementia. These patterns across age will need to be substantiated in larger, longitudinal datasets, but the current study represents a cross-sectional foundation upon which predictions in such studies may be based. The data indicates that isolated cognitive and EEG/ERP markers would not be sufficient to determine specific profiles for AD and MCI groups. Yet when cognitive and psychophysiological measures are considered conjointly in the same subjects, they reflect patterns of critical change that precipitates decline into diagnosable dementia that is not easily detected by clinical assessment tools [72]. In particular, the correlation of resting EEG with cognitive measures could be used to identify those patients in preclinical phases or even normal subjects who are at higher-risk for conversion to AD, by taking their age into account. An integrative approach may lead to greater understanding of the pathology of degeneration, where differences between sub-types of dementia for instance, may be able to be objectively quantified.

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