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Research Report

EEG MARKERS FOR COGNITIVE DECLINE IN ELDERLY SUBJECTS WITH SUBJECTIVE MEMORY COMPLAINTS

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New treatments for Alzheimer's disease require early detection of cognitive decline. Most studies seeking to identify markers of early cognitive decline have focused on a limited number of measures. We sought to establish the profile of brain function measures which best define early neuropsychological decline. We compared subjects with subjective memory complaints to normative controls on a wide range of EEG derived measures, including a new measure of event-related spatio-temporal waves and biophysical modeling, which derives anatomical and physiological parameters based on subject's EEG measurements. Measures that distinguished the groups were then related to cognitive performance on a variety of learning and executive function tasks. The EEG measures include standard power measures, peak alpha frequency, EEG desynchronization to eyes-opening, and global phase synchrony. The most prominent differences in subjective memory complaint subjects were elevated alpha power and an increased number of spatio-temporal wave events. Higher alpha power and changes in wave activity related most strongly to a decline in verbal memory performance in subjects with subjective memory complaints, and also declines in maze performance and working memory reaction time. Interestingly, higher alpha power and wave activity were correlated with improved performance in reverse digit span in the subjective memory complaint group. The modeling results suggest that differences in the subjective memory complaint subjects were due to a decrease in cortical and thalamic inhibitory gains and slowed dendritic time-constants. The complementary profile that emerges from the variety of measures and analyses points to a nonlinear progression in electrophysiological changes from early neuropsychological decline to late-stage dementia, and electrophysiological changes in subjective memory complaint that vary in their relationships to a range of memory-related tasks.

Keywords: Subjective memory complaint; cognition; EEG; traveling waves; biophysical model; neural synchrony; international database.

1. Introduction

1.1. *Early detection of cognitive decline using EEG*

Alzheimer's disease (AD) represents one of the most daunting disorders of advanced age. AD is by far the most common cause of severe cognitive impairment among people older than 65 years of age, and at present, treatment options are often limited to the earliest stages of the disease. As such, there has been intense effort focusing on identifying individuals with the highest risk of developing AD, in order to provide therapeutic options as early as possible in the course of the disease.

Previous studies have consistently revealed that elderly individuals with subjective memory complaints (SMC) are at elevated risk for subsequent development of AD [1, 2]. This is especially true among older individuals with lower baseline cognitive scores [3]. Baseline characteristics of individuals with SMC reveal significant differences in hippocampal volume [4], a finding consistent with the early neuropathology of Mild Cognitive Impairment (MCI) and AD. Individuals with SMC perform more poorly on neuropsychological tests of verbal memory, compared to individuals without complaints, but objective evidence of cognitive difficulties are not universally evident among those with SMC [5]. Importantly, however, individuals with SMC have also reported greater depression scores compared with matched controls [6], suggesting that psychosocial factors may contribute to heterogeneity in this population.

In the earliest stages of MCI and AD, the EEG is often normal [7]. Other studies suggest that the earliest stages of AD are marked by an increase in theta activity and a decrease in beta activity [8]. Maximal differences between presenile and normal controls have previously been detected in the right posterior temporal area [9]. Event Related Potential (ERP) measures have shown utility in predicting the conversion to dementia among elderly individuals at risk for AD. Gironell and colleagues [10] examined 94 individuals with SMC using ERP P300 latency at baseline, and then again at 24-month follow-up. The results revealed that P300 latency was delayed among individuals who were eventually diagnosed with AD.

Overall, these findings are encouraging and suggest that neurophysiological markers of brain dysfunction may provide sensitive indices of early degenerative disease, though improved sensitivity and specificity would offer greater clinical utility. Previous studies tend to be limited by the small number of variables studied. Meta-reviews provide a useful method of integrating literature, but are limited by the heterogeneity of both subject populations and the measures employed, as well as variations in experimental tasks across studies.

1.2. *Synchrony and spatio-temporal waves*

A number of measures of synchrony in the EEG have been applied to the study of the progression of AD. These include coherence, global field synchronization [11], synchronization likelihood [7] and spatio-temporal waves [12]. Indices measuring

the dynamics of the EEG have demonstrated utility in identifying subjects prior to onset of AD. Decreased global field synchronization in the alpha, beta and gamma frequency bands has been recently reported for individuals with MCI [11]. However, another study has shown in a visual working memory task that synchronization likelihood was lower in AD than SMC at 10–12 Hz and 12–30 Hz, but higher in MCI than SMC at 8–10 Hz [7]. This mixed pattern of results suggests that during the early stages of cognitive decline, an increase in synchronization can occur.

In this study, we utilize a measure of global phase synchrony [13] to assess synchronization of phase across the whole scalp in the frequency ranges of delta to beta. This measure is similar in concept to other global measures of phase synchronization (e.g. Ref. 11). This study also utilizes a new measure of spatio-temporal waves, which are the cortical equivalent to waves on a pond spreading from a dropped stone. A number of studies have shown the behavior of spatio-temporal waves in scalp EEG to be task dependent, including working memory [14], listening to auditory tones [12], resting states [15] and sleep [16]. In each of these studies, the spatio-temporal waves had long spatial-wavelength and showed smooth changes in phase across the scalp (phase-gradients) at each snap-shot in time. The measure of spatio-temporal waves in the present study makes use of the properties of long spatial wavelength and smooth phase-gradients to detect the waves.

1.3. *Biophysical modeling*

In this paper, we also use a biophysical model of the EEG that provides estimates of primary physiological parameters, based on the measured EEG of the subject. The EEG model is a continuum based model, which has been developed from earlier work by a number of authors [17–31]. The recent application of this approach directly models the EEG in the form of mean-field potentials, using primary neurophysiological principles and structures, including axonal transmission delays, synapto-dendritic rates, separate excitatory and inhibitory neural populations, firing thresholds, nonlinearities, range-dependent connectivities, and cortical and thalamo-cortical networks [32–36]. By modeling the EEG waveforms and spectra, and auditory event related potentials (ERPs), the biophysical model illuminates how primary networks contribute to cortical dynamics. In particular, the modeling has revealed the importance and strength of thalamo-cortical inputs and its influence upon cortical dynamics [32–34, 36]. The results from the EEG model thus provide a potential insight into the mechanisms' underlying differences in EEG between the SMC and normative subjects.

1.4. *Integrating brain function and cognitive measures in detecting early cognitive decline*

Given the limited number of studies directly comparing the EEG of SMC subjects with matched controls, and the contradictory nature of some previous results, we

formulated working hypotheses for this study based on this work, as well as that from AD. We proposed that SMC subjects would also show a decrease in fast wave EEG, but an increase in slow wave EEG. In line with the bulk of findings for the dynamical measures of brain activity, there should also be a decrease in global phase synchrony and wave-activity. Given that SMC has been associated with verbal memory problems in particular [5], we expected the brain function changes to specifically relate to problems in verbal memory performance, and to other memory-related tasks. Drawing on evidence that implicates the hippocampal-prefrontal networks in MCI and AD [4], we proposed that biophysical modeling would reveal physiological changes in subcortical to cortical connections.

To test these working hypotheses, we first compared the groups on EEG related measures. Psychophysiological variables showing between group differences were then correlated with memory-related cognitive variables within the SMC group. Significant relationships between psychophysiology and cognition for the SMC group were then verified by comparing the cognitive scores between the groups.

2. Methods

2.1. *Subjects*

One hundred healthy elderly subjects with subjective memory complaints (mean age of 64.9 years, SD = 8.7, range 52–88 years) were recruited by Health and Cognizance LLC via an advertisement in the local newspapers. Of the initial 300+ respondents, only 100 remained after the application of the initial exclusion and inclusion criteria. Exclusion criteria included a personal history of mental illness [or a family history of Attention Deficit Hyperactivity Disorder (ADHD), Schizophrenia, Bipolar Disorder, or genetic disorder], physical brain injury, neurological disorder or other serious medical condition and/or a personal history of drug or alcohol addiction. Subjects were also excluded if they were using psychoactive drugs such as antidepressants or sleep medication. In addition to the exclusion criteria, the following inclusion criteria were used:

- age of 52 years or older,
- complaint of memory problems that have been increasing over time,
- confirmation by a close family member that the subject displayed increasing memory problems over time, and
- ability to engage in hobbies and other normal daily activities.

All subjects voluntarily signed a written informed consent. Subjects were additionally required to refrain from caffeine, alcohol and smoking for at least 2 hours prior to testing. When subjects met inclusion and exclusion criteria, they were assessed by the Brain Resource Company B.V. Laboratory in Nijmegen, The Netherlands.

Two subjects from the SMC group were excluded due to incomplete data. Another two subjects were excluded since they were diagnosed with Alzheimer's

disease by the department of Gerontology of the Radboud Hospital Nijmegen. These two subjects had a CDR score of 1 and were clinically assessed by a licensed Neuropsychologist and Psychiatrist, in addition to the screenings performed for this study. Seventeen subjects were excluded since they had a GDS score greater than 11, indicating that subjects were experiencing significant depressive symptomatology [37–40]. Data from the 79 remaining SMC subjects were included in this study.

The control group consisted of 30 Dutch subjects, and 49 subjects from other countries were selected from a pool of 540 normative subjects aged above 50. Dutch controls were sought first, but once controls could not be found within 5 years of age, the remaining subjects were taken from the international control group. All controls were gender matched. The exclusion criteria for the controls were the same as for the SMC group. The average age of the control group was 63.1 years (SD = 7.9), which was not significantly different to the SMC group.

2.2. *Neuropsychology and clinical tests*

Subjects were seated in a sound and light attenuated room, controlled at an ambient temperature of 22°C behind a touch screen monitor and were assessed on a profile of cognitive (neuropsychological) domains (See [43, 44] for details of these tests). This battery of tests has good test-retest reliability [45] and established norms [46]. An outline of these tests is provided below.

Visual Working Memory: This task consists of a series of letters (B, C, D or G) presented to the subject on the computer screen (for 200 ms), separated by an interval of 2.5 seconds. If the same letter appears twice in a row, the subject is asked to press buttons with the index finger of each hand. Speed and accuracy of response are equally stressed in the task instructions. There are 125 stimuli presented in total, 85 being non-target letters and 20 being target letters (i.e., repetitions of the previous letter). The task is designed to assess working memory and attention processes. This task lasts approximately 6 minutes.

Memory Recall: The memory recall task assesses the verbal learning and memory of the subject. The subject is presented verbally with a list of 12 words which they are asked to memorize. The list contains 12 concrete words from the Dutch or English language. Words are closely matched on concreteness, number of letters and frequency. Subjects were tested in their primary language. The list is presented 4 times in total and the subject is required to recall as many words as possible after each presentation. The subject is then presented with a list of distracter words and asked to recall those. The subject is then asked to recall the 12 words from the original list. Approximately 25 minutes later, the subject is again asked to recall the 12 words from the original list. This task takes approximately 6 minutes of the total time.

Digit span: In this test, the subject sees on the screen a series of digits (4, 2, 7 etc., 500 ms presentation), separated by a one second interval. The subject is then

immediately asked to enter the digits on a numeric keypad on the touch-screen, either in forward order or backwards (in the case of reverse digit span). The number of digits in each sequence is gradually increased from 3 to 9. The score on this test is given by the maximum number of digits the subject can reliably repeat without making mistakes. The digit span test taps one of the basic capacities of the short-term memory system and working memory for the backwards digit span. This task takes approximately 5 minutes.

Executive Maze Task: The subject is presented with a grid (8×8 matrix) of circles on the computer screen. The object of the task is to find the hidden path through the grid, from the beginning point at the bottom of the grid to the end point at the top. The subject is able to navigate around the grid by pressing arrow keys. The subject is presented with one tone (and a red cross at the bottom of the screen) if they make an incorrect move, and a different tone (and a green tick at the bottom of the screen) if they make a correct move. Each time the subject does the task, the maze is the same. The purpose of the task is therefore to assess how quickly the subject learns the route through the maze and their ability to remember that route. The maze task is 8 minutes maximum in duration.

Subjects were assessed on the MiniMental Status Exam (MMSE) [47] and Geriatric Depression Scale (GDS) [48]. In assessing the MMSE, both questions, i.e., counting back from one hundred in steps of seven numbers and spelling the word "dorst" were posed to all the subjects, regardless of their performance of the first question, for the sake of standardization (highest score was used in the final summation score). MMSE data were age and education corrected, as suggested in Refs. 49 and 50, by adding 1 MMSE point if subjects were older than 75 years old or had less than 8 years of education. One MMSE point was subtracted if subjects had more than 14 years of education. The GDS was assessed to measure the level of depressive symptoms. Subjects were required to answer the 30 questions on how they felt over the last 2 weeks.

2.3. *Electroencephalographic data acquisition*

Participants were seated in a sound and light attenuated room, controlled at an ambient temperature of 22°C. EEG data were acquired from 26 channels: Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, C3, Cz, C4, T4, CP3, CPz, CP4, T5, P3, Pz, P4, T6, O1, Oz and O2, using a Quikcap, NuAmps and according to the 10–20 electrode international system. Data were referenced to an additional cephalic site and an average-referenced offline. Horizontal eye-movements were recorded with electrodes placed 1.5 cm lateral to the outer canthus of each eye. Vertical eye movements were recorded with electrodes placed 3 mm above the middle of the left eyebrow and 1.5 cm below the middle of the left bottom eye-lid. Skin resistance was < 5 K Ohms and > 1 K Ohm for all electrodes. A continuous acquisition system was employed and EEG data were EOG corrected offline [41]. The sampling rate of all channels

was 500 Hz. A low pass filter with an attenuation of 40 dB per decade above 100 Hz was employed prior to digitization.

The EEG data were recorded for two minutes during each of eyes open (EO) and eyes closed (EC) conditions. Subjects were asked to sit quietly with either eyes open and fixed on a red dot presented on a computer screen, or in EC condition, with eyes closed. EEG was also recorded during the Visual Working Memory task previously described.

Average power spectra were computed for each resting condition (EO, EC). Each two-minute epoch was divided into adjacent intervals of four seconds. Power spectral analysis was performed on each four second interval by first applying a Welch window to the data, and then performing a Fast Fourier Transform (FFT). The power was calculated in the four frequency bands for both conditions, delta (1.5–3.5 Hz), theta (4–7.5 Hz), alpha (8–13 Hz), and beta (14.5–30 Hz). The power data were then logarithmically transformed in order to fulfill the normal distributional assumptions required for parametric statistical analysis.

EEG reactivity to eyes opening was also calculated, which was defined as the logarithm of the power in each band during the EO condition, minus the logarithm of the power in the EC condition. This phenomenon is known as the effect of alpha blocking or alpha desynchronization, with the processing of visual stimuli. Predominant changes are observed as a significant reduction in alpha band power, but an increase in lower and higher frequency bands [41]. Dementia related conditions have been considered to cause difficulty in maintaining a state of alpha desynchronization, resulting in poor task performance [42].

2.4. *Statistical analysis of cognitive and EEG power variables*

Differences between groups on neuropsychological and EEG power variables were analyzed using the Statistical Package for Social Science (SPSS v.12) Analysis of Variance (ANOVA) procedure. For the EEG power variables, as a large number of statistical tests were conducted to enable inclusion of every electrode site, results are reported only for those measures where four contiguous electrodes were significant ($p < 0.05$). Where significant differences were found between the groups, correlational analyses were undertaken for the SMC group to look for patterns of association between psychophysiological and cognitive/behavioral measures related to memory. To allow for the potential heterogeneity of the SMC group, partial correlations controling GDS or MMSE scores were also carried out. Results were only included if they indicated both a significant difference in psychophysical measures between the two groups and when the psychophysical measures were significantly correlated with cognitive measures related to memory and executive functions.

2.5. *Phase synchrony and phase-gradients*

The EEG data for working memory backgrounds were analyzed using a measure of phase synchrony, described in detail elsewhere [13]. In short, phases are computed

for each time-sample and frequency at each electrode, and synchrony between sites at a given frequency computed as $1 - \sigma_c^2$, where σ_c^2 is the circular variance. The main difference in the present work is that wavelet analysis rather than the FFT was used to estimate the phases at a given frequency. The phases were estimated for 30 logarithmically spaced frequency bands between 0.2 and 32 Hz. The phases were estimated at 10 ms intervals between −200 and 800 ms within each working memory trial, where zero is the time of stimulus onset. There are two advantages to the use of wavelet analysis in the present research, which assesses event-related, low to mid frequency phase synchrony. Firstly, the phases can be estimated for arbitrary frequencies using suitably scaled daughter wavelets. This enables more frequency bands in the lower frequency ranges to be sampled than FFT methods allow. Secondly, the temporal resolution of the phase estimation, using wavelets scales with frequency. Since event-related changes in phase synchrony at lower frequencies persist for only a cycle or two, the event-related synchrony measure becomes temporally blurred if FFT is used to estimate the phases. For this reason, a *two* cycle Morlet wavelet was also used. Whilst this entailed a large frequency bandwidth, testing with surrogate data showed a wavelet with this number of cycles to be optimal in the trade-off between frequency bandwidth and capturing short, even-related changes in the phase synchrony.

For the spatio-temporal wave measure, the phases at each electrode site were estimated in a manner identical to the phase synchrony measure. Comparisons to surrogate data have shown that during episodes of spatio-temporal waves, the waves have long spatial wavelength compared with the size of the scalp (i.e., the phase fall within a limited range, usually within π). The electrode phase values at a given time, sample and frequency can therefore be assigned a temporal ordering from a phase-leading site to the most phase-lagged site. For each time sample and at each frequency, the phases at each electrode were converted into relative phases by referencing the phase relative to the phase-leading electrode.

The spatial patterns of relative phases were assessed using three phase-gradient basis functions. These basis functions are smoothly changing gradients across the scalp. The three basis functions comprise of an anterior to posterior basis function, a peripheral to central basis function and a right to left basis function. Linear combinations of these phase-gradient basis functions enable a wide range of smoothly changing patterns of phase-gradient to be characterized, each having the property of having only one minima or one maxima. The amount of variance explained in the pattern of relative phases across the scalp by the phase-gradient basis functions is given by

$$\sigma_{\mathrm{M}\Psi}^2 = \rho(\mathrm{M}\Psi, \Psi)^2$$

where $\mathrm{M}\Psi$ is the linear combination of basis functions that gives the best fit, Ψ is the pattern of relative phases across the scalp, ρ is the correlation function, and $\sigma_{\mathrm{M}\Psi}^2$ is the amount of variance explained. The specific organization of patterns of phase-gradient can be assessed by calculating the correlation of the relative phases

with each of the individual basis functions at each time sample and frequency. For example, r_{AP} denotes the correlation of the relative phases with the anterior to posterior basis function. The presence of phase-gradients in the scalp EEG coincides with the presence spatio-temporal waves of short duration, i.e., usually no longer than one complete temporal cycle.

The detailed differences between the SMC group and controls in the phase synchrony and phase-gradient measures were explored using multiple t-tests over the entire range of time and frequency points sampled. In addition, the detailed patterns of correlation between phase-gradient measures for the SMC group with cognitive and behavioral measures were explored using multiple correlations over the entire range of time and frequency points. Due to the large number of statistical tests this entails, the multiple t-tests and correlations were only included in the results if they were significant at the $p < 0.05$ level, over 20 contiguous time and/or frequency points. Results for the phase-gradient measures had to meet this criterion in both the between groups t-tests and the SMC group correlations to be counted as significant in this study.

2.6. *Biophysical modeling*

The structure of the model is reflected in a modest number of neurophysiological parameters, which must lie within published plausible physiological limits [51, 35, 36]. The model parameters appeared in the expression for the theoretical EEG spectrum used in inverse modeling of experimental EEG data [35, 36]. For brevity, the equations and numerical details have been omitted. These, including the complete methodology, are summarized in a prior issue of this journal [35, 36, 52], and the full mathematical analysis is also given elsewhere [33, 28, 34, 36]. The physiological features used in the model have also been justified in previous studies [26, 53, 33, 36].

The architecture of the model is illustrated in Figs. 1 and 2. Figure 1 shows the detailed physiological components of a single unit in the model. Figure 2 depicts the model's primary pathways and structures from which EEG rhythms such as alpha and theta can arise, whereas local neuronal populations are associated with higher frequency rhythms such as gamma. The neural activity of the primary pathways is accounted for in terms of the gains which parametrize the differential number of neural pulses out per pulse in, and describe the effect of input perturbations from the various afferent neural fields ϕ_b on the firing rate Q_a of excitatory and inhibitory neurons ($a = i, e$) [26, 33].

The data fitting procedure was similar to that detailed in [35, 36]. For model fitting, $\log_e$ of the sum P_{est} of the theoretical EEG and EMG spectra was fitted to $\log_e P_{\text{exp}}$ (experimental spectra), measured at a single site (Cz in the present research). Logarithms were taken to permit each frequency decade to be weighted approximately equally, thereby maintaining fits based on spectral detail rather than

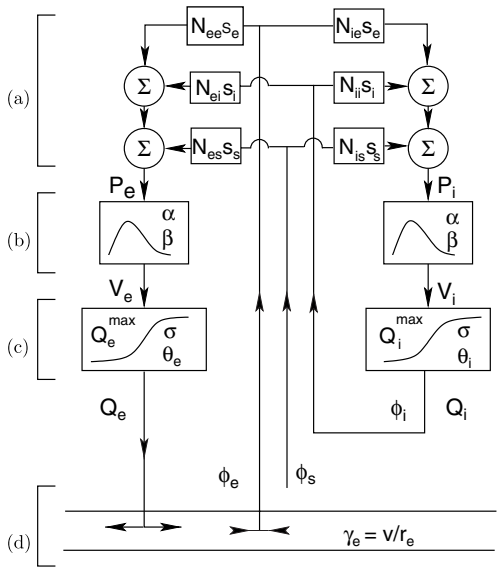


Fig. 1. Mathematical Summary of the Biophysical Model. This schematic shows the interconnection of a single cortical unit with excitatory neuron on the left and an inhibitory neuron on the right. The four transformations that occur within neurons are represented by boxes: (a) spatial summation of pulse density fields ϕ_b $(b = i, e, s)$ from inhibitory and excitatory subcortical (s, or thalamic relay) and cortical neurons (i, e), and a multiplication of afferent action potentials by synaptic numbers Nab and strengths sb; (b) synapto-dendritic activity parametrized by dendritic rate constants α and β induces perturbations of the somatic membrane potential Va $(a = e, i)$ at the cell body; (c) resulting in firing rate Qe, which is related to the membrane potential Va by a typical sigmoidal function, characterized by threshold θa, width σa, and maximum firing rate $Q_a^{\max}$; and (d) propagation of excitatory impulses throughout the cortex as fields ϕa along axons according to a 2-D wave equation with damping rate γe parametrized by conduction velocity and axonal range [35].

the number of data points [36]. The error between P_{est} and P_{exp} was reduced by the Monte Carlo parameter optimization.

3. Results

3.1. *EEG power and cognition*

In the eyes-open condition, the SMC group showed greater alpha power across the majority of the scalp (particularly frontal $p < 0.01$). No significant group differences were found for the beta, delta and theta bands that satisfied the criteria of 4 adjacent sites with $p < 0.05$. For the eyes closed condition, the SMC group showed greater alpha power for most sites (particularly frontal $p < 0.01$), greater beta power (14 central and parietal sites $p < 0.05$, 4 sites frontal $p < 0.01$) and greater theta power (frontally, $p < 0.05$). The SMC group showed markedly greater eyes-closed alpha peak-power (fronto-centrally) — i.e., the *power* at the individual alpha peak frequency for subjects in the SMC group. The grand-average curves for spectral

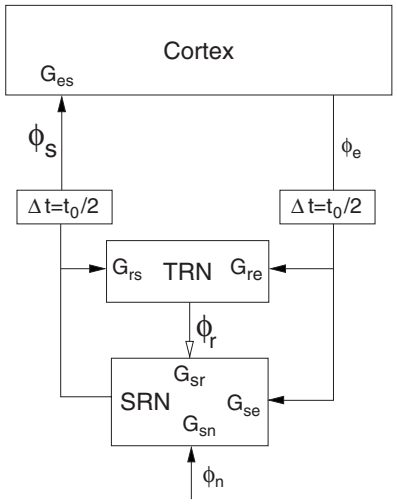


Fig. 2. Schematic showing primary pathways between the cortex, specific and secondary relay nuclei (SRN) and the thalamic reticular nucleus (TRN). The interconnections are shown with arrows; either solid (excitatory) or open (inhibitory). These provide two partially overlapping cortico-thalamocortical feedback pathways: one direct and excitatory (+) between the cortex and SRN with total gain $G_{ese} = G_{es}G_{se}$; and one indirect and inhibitory (−) pathway from cortex to TRN to SRN to cortex with total gain $G_{esre} = G_{es}G_{sr}G_{re}$. Intrathalamic feedback between the TRN and SRN is also possible, with gain $G_{srs} = G_{sr}G_{rs}$. Propagation between cortex and thalamus involves delays of $t_0/2$ (~ 40 ms), and additional small delays are induced by each nucleus due to synapto-dendritic filtering. The firing rate in each pathway is ϕ_a, $a = e$, r, s and ϕ_N is an independent source of signals [35].

power are shown in Fig. 3. The graph shows that the SMC group had higher alpha band power, and higher power at the peak alpha frequency. There were no group differences in the eyes-closed delta band.

EEG reactivity to the opening of the eyes was also measured. The SMC participants showed differences for EEG reactivity in the delta band at central and posterior sites ($p < 0.05$). The SMC subjects showed a slight decrease in delta activity to eyes opening, whereas the controls showed a slight increase in delta activity. There were also differences for left-frontal and central beta power ($p < 0.01$), with SMC subjects showing a greater beta power decrease to eyes opening. Comparisons of reactivity scores across the theta and alpha bands were not significant.

The EEG power measures that showed differences between the SMC and control groups were correlated with cognitive and behavioral variables within the SMC group. There were significant positive correlations between the psychophysical variables of EEG alpha and theta power, peak alpha power and GDS scores. Increases in EEG power and peak alpha scores are associated with higher levels of depression in the non-clinical range. These same psychophysiological variables correlated positively with maze completion time, i.e., poor maze performance. There were significant negative correlations between these three psychophysiological variables and the total number of words recalled in the memory task in trials 1–4, such that increases

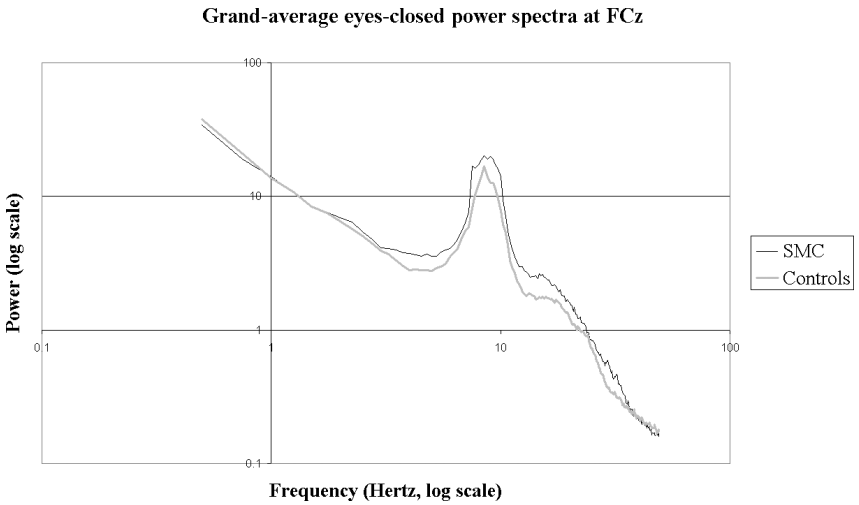


Fig. 3. Grand-average spectral power for electrode FCz. The graph shows that the SMC group had higher alpha band power, and higher alpha power at peak alpha frequency.

in peak alpha were associated with poorer recall in early trials. The memory recall on trial 6 showed even stronger pattern of correlations with the power variables. These correlations are shown in Table 1. The strongest correlations occurred for eyes-open alpha power at peak alpha frequency and verbal recall scores.

There were significant correlations between GDS scores and eyes-closed alpha power at peak alpha frequency (Fp1, $r = 0.212$; F7, $r = 0.282$; F3, $r = 0.253$; Fz, $r = 0.224$; F4, $r = 0.220$; FC3, $r = 0.269$; FCz, $r = 0.215$; FC4, $r = 0.204$). There were significant correlations between EEG reactivity in the delta band and GDS scores (CP3, $r = -0.225$; CPz, $r = -0.235$; Cz, $r = -0.204$; P3, $r = -0.200$; P4, $r = -0.205$; Pz, $r = -0.252$). There was also a pattern of significant positive correlations between EEG resting (eyes closed) beta (parietal) and alpha (midline) power, and reverse digit span score. Here increases in power were associated with a higher span (Beta: P3, $r = 0.210$; Pz, $r = 0.217$; P4, $r = 0.202$; Alpha: FCz, $r = 0.215$; Cz, $r = 0.223$; C4, $r = 0.208$; CP4, $r = 0.211$; P4, $r = 0.204$).

There was no pattern of association between the EEG power variables and forward digit span performance or working memory reaction time. In general, controling for MMSE and GDS did not weaken the patterns of correlations reported here. For verbal memory recall and reverse digit span, the strength of the reported correlations with EEG power variables generally increased, when controling for either MMSE or GDS.

3.2. *Phase synchrony and phase-gradients*

There were significant differences between the groups for the phase-gradient measures. Figure 4(a) shows the grand-average values of $\sigma^2_{\mathrm{M}\Psi}$ for the control group during the working memory task, for the backgrounds condition. There is a peak in

Table 1. Significant correlations between power measures and cognitive variables. Numbers indicate r values. Correlations significant at $p < 0.05$ are *italicized* and shaded, $p < 0.01$ ***italicized and bold*** and shaded. The table contains all significant correlations, according to the criteria outlined in the methods section, not explicitly enumerated in the main text.

	GDS	Maze Time to Completion	Verbal Recall trials 1–4	Verbal Recall trial 6
Eyes-open alpha				
Fp1	*0.257*	*0.313*	−0.186	*−0.306*
Fp2	*0.255*	*0.332*	*−0.204*	*−0.310*
F7	*0.242*	*0.278*	*−0.228*	*−0.385*
F3	*0.250*	*0.260*	−0.179	*−0.315*
Fz	*0.217*	*0.223*	−0.160	*−0.302*
F4	*0.242*	*0.265*	−0.183	*−0.314*
F8	*0.257*	*0.343*	*−0.208*	*−0.353*
FC3	*0.219*	*0.231*	−0.179	*−0.279*
FCz	*0.232*	*0.213*	−0.165	*−0.304*
FC4	*0.242*	*0.239*	−0.179	*−0.292*
T3	*0.232*	*0.303*	*−0.221*	*−0.378*
C3	*0.218*	*0.240*	−0.144	*−0.232*
Cz	*0.224*	*0.212*	−0.147	*−0.269*
C4	*0.254*	*0.223*	−0.141	*−0.252*
CP3	*0.233*	*0.224*	−0.149	*−0.215*
CPz	*0.201*	0.194	−0.136	*−0.216*
CP4	*0.250*	*0.205*	−0.134	*−0.222*
P3	*0.258*	0.198	−0.122	−0.194
Pz	*0.226*	0.183	−0.104	−0.188
P4	*0.252*	0.189	−0.121	−0.200
O1	*0.275*	*0.325*	−0.048	−0.175
Oz	*0.242*	*0.326*	−0.020	−0.159
Eyes-closed theta				
Fp1	*0.208*	*0.330*	*−0.220*	*−0.274*
Fp2	*0.214*	*0.320*	*−0.208*	*−0.282*
F3	*0.248*	*0.242*	−0.175	*−0.298*
Fz	*0.223*	*0.221*	−0.140	*−0.281*
Eyes-open alpha power at peak frequency				
Fp1	*0.251*	0.170	*−0.245*	*−0.299*
Fp2	*0.326*	*0.203*	*−0.265*	*−0.274*
F7	*0.330*	*0.262*	***−0.425***	***−0.443***
Fz	*0.223*	0.125	*−0.259*	*−0.285*
F8	*0.314*	*0.214*	*−0.342*	*−0.349*

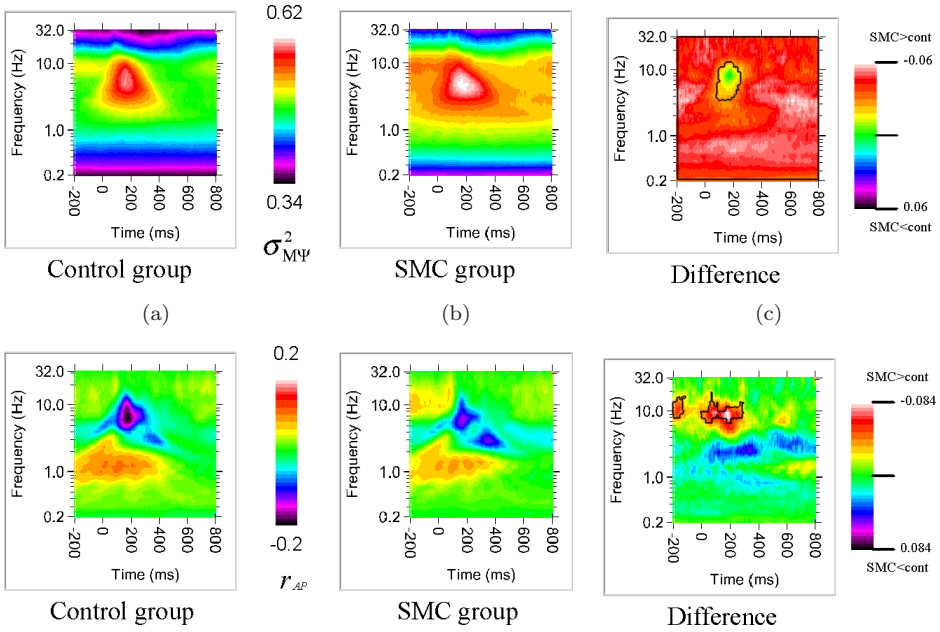


Fig. 4. Time by frequency plots for two different phase-gradient measures during the working memory task, backgrounds condition. $\sigma^2_{M\Psi}$ is the amount of variance explained by the phase-gradient model, and r_{AP} is the correlation of the relative phases with the anterior to posterior basis function. Time is represented along the x-axis, with stimulus delivery at time equals zero. Frequency is represented along the y-axis, which is logarithmically scaled. Centre frequencies of the bands used in the analysis are indicated by breaks in the dashed line along the left edge of the plot. Regions satisfying the criteria of significance — at least 20 contiguous time and/or frequency points with $p < 0.05$, are contained within the black lines.

(a) The stimulus-locked grand-average $\sigma^2_{M\Psi}$ for the control group, showing a large increase in the amount of variance explained by the phase-gradient model at $\sim$170 ms, $\sim$6 Hz. The scale to the right of the plot shows the grand-average variance explained by the phase-gradient model.
(b) The stimulus-locked grand-average $\sigma^2_{M\Psi}$ for the SMC group, showing the same peak in $\sigma^2_{M\Psi}$ at $\sim$170 ms, $\sim$6 Hz, but also higher values of $\sigma^2_{M\Psi}$ at most times and frequencies. The scale is the same as in (a).
(c) Difference of means in $\sigma^2_{M\Psi}$ for the two groups, showing a significant increase in $\sigma^2_{M\Psi}$ **outside** the region neighboring $\sim$170 ms, $\sim$6 Hz for SMC.
(d) The stimulus-locked grand-average r_{AP} for the control group, showing that the peak in $\sigma^2_{M\Psi}$ at $\sim$170 ms, $\sim$6 Hz is associated with posterior to anterior phase-gradients. The scale to the right of the plot shows the grand-average correlation values between the relative phases and the r_{AP} basis function.
(e) The stimulus-locked grand-average r_{AP} for the SMC group, showing a weaker tendency for posterior to anterior phase-gradients at $\sim$170 ms, $\sim$6 Hz. The scale is the same as in (d).
(f) Difference of means in r_{AP} for the two groups, showing a significant increase in r_{AP} in the region of $\sim$170 ms, $\sim$6 Hz. This increase is due to a weaker tendency for the SMC group to engage in posterior to anterior phase gradients.

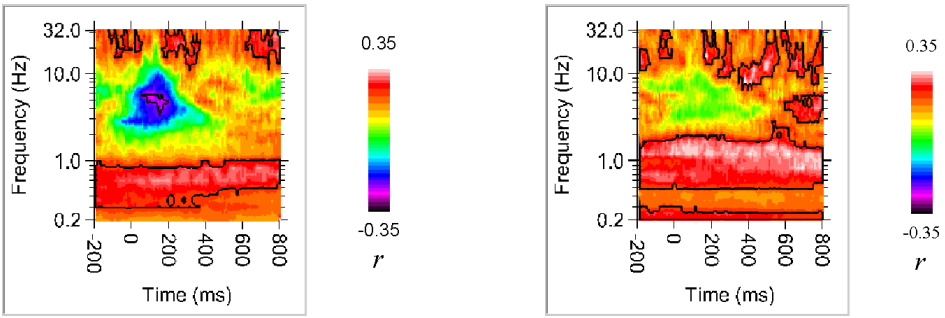
$\sigma^2_{\mathrm{M}\Psi}$ at $\sim$170 ms, $\sim$6 Hz that is associated with this task. Also, Fig. 4(d) shows the control group grand-average r_{AP} measure — the correlation of the relative phases with the anterior to posterior basis function. The negative values of grand-average r_{AP} at $\sim$170 ms, $\sim$6 Hz indicate that the peak in $\sigma^2_{\mathrm{M}\Psi}$ was associated with a posterior to anterior phase-gradient. The other basis functions showed no relationship to the main peak in $\sigma^2_{\mathrm{M}\Psi}$.

The SMC group had greater values of mean $\sigma^2_{\mathrm{M}\Psi}$ over a range of times and frequencies outside the event-related peak in $\sigma^2_{\mathrm{M}\Psi}$, for the working memory backgrounds task. This difference between the groups in the phase-gradient measure was explored using multiple t-test comparisons. Figure 4(c) shows that outside the region neighboring $\sim$170 ms, $\sim$6 Hz, the SMC group had greater values of $\sigma^2_{\mathrm{M}\Psi}$. This result indicates an excess of spatio-temporal waves activity outside the peak time/frequency region associated with the task. The SMC group had greater values of mean r_{AP} in the region neighboring $\sim$170 ms, $\sim$6 Hz. Figure 4(f) shows that this was due to a decreased engagement of posterior to anterior phase-gradients in the SMC group. For the SMC group, there was also an increased engagement in phase-gradients with a posterior to anterior component at 500–700 ms and 3–4 Hz, but this was unrelated to the main event-related peaks in $\sigma^2_{\mathrm{M}\Psi}$ or r_{AP}.

Figure 5(a) shows the correlations for the SMC group between mean $\sigma^2_{\mathrm{M}\Psi}$ during the working memory task (backgrounds) and the reaction time to the target stimuli. The GDS score of the SMC subjects was controlled for in these correlations, and did not change the results nor did controling for MMSE (not shown). Reaction time was positively correlated with mean $\sigma^2_{\mathrm{M}\Psi}$ near the event-related peak in $\sigma^2_{\mathrm{M}\Psi}$ at $\sim$170 ms, 6 Hz. Conversely, reaction time was negatively correlated with mean $\sigma^2_{\mathrm{M}\Psi}$ in the beta range and in the sub-delta, slow wave range. This finding suggests that SMC subjects with $\sigma^2_{\mathrm{M}\Psi}$ profiles more typical of the controls — high $\sigma^2_{\mathrm{M}\Psi}$ at the event-related peak and low $\sigma^2_{\mathrm{M}\Psi}$ elsewhere, had faster reaction times to working memory target stimuli.

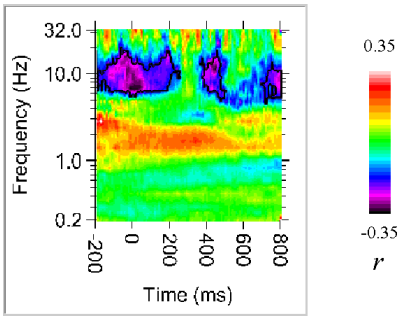
Figure 5(b) shows the correlations for the SMC group between mean $\sigma^2_{\mathrm{M}\Psi}$ during the working memory task (backgrounds) and the reverse digit span scores. The GDS score of the SMC subjects was controlled for in these correlations and did not change the results, nor the controling for MMSE. Interestingly, high mean $\sigma^2_{\mathrm{M}\Psi}$, at a range of times and frequencies outside the event-related peak in $\sigma^2_{\mathrm{M}\Psi}$ were *positively* correlated with reverse digit span scores in the SMC group. The relevant frequencies included slow-wave activity, as well as the delta, theta, alpha and beta bands. This finding did not arise in the control group, nor did it arise in the digit span task in either groups (i.e., the less demanding forward version of the task).

Figure 5(c) shows the correlations for the SMC group between mean r_{AP} during the working memory task (backgrounds) and the total verbal learning score. There were significant positive correlations over several time intervals between the frequencies 6 and 20 Hz. An important aspect of this finding is that the significant correlation in the region surrounding $\sim$170 ms, $\sim$6 Hz drops to merely a trend level, when the effects of GDS are controlled for in the correlations, whereas the other time



(a) Correlations between $\sigma^2_{\mathrm{M}\Psi}$ for Visual Working Memory and reaction time (controlling for GDS)

(b) Correlations between $\sigma^2_{\mathrm{M}\Psi}$ for Visual Working Memory and reverse digit span (controlling for GDS)



(c) Correlations between r_{AP} for Visual Working Memory and verbal learning score

Fig. 5. Time by frequency plots of the correlations for the SMC group between phase-gradient measures during the working memory task, backgrounds condition, and several of the cognitive and behavioral measures. Figure conventions are the same as for Fig. 4.

(a) Correlations between $\sigma^2_{\mathrm{M}\Psi}$ and reaction time in the working memory task, backgrounds condition, controling for the effects of GDS score. Subjects in the SMC group showed good performance (decreased reaction time) if they had high $\sigma^2_{\mathrm{M}\Psi}$ values in the region neighboring ~ 170 ms, ~ 6 Hz. The SMC group showed poor performance (increased reaction time) if they had high $\sigma^2_{\mathrm{M}\Psi}$ values outside the region neighboring ~ 170 ms, ~ 6 Hz. This latter effect was significant in the sub-delta (slow-wave) and beta bands.

(b) Correlations between $\sigma^2_{\mathrm{M}\Psi}$ during the working memory task, backgrounds condition and reverse digit span, controling for the effects of GDS score. Subjects in the SMC group had higher reverse digit span scores if they had high $\sigma^2_{\mathrm{M}\Psi}$ values outside the region neighboring ~ 170 ms, ~ 6 Hz. This effect was significant across a wide range of times and frequencies.

(c) Correlations between r_{AP} during the working memory task, backgrounds condition and verbal memory score. SMC subjects with higher verbal memory scores also had task relevant increases in posterior to anterior phase-gradients at ~ 170 ms, ~ 6 Hz during the working memory task, backgrounds condition. This correlation was not significant in the region immediately neighboring ~ 170 ms, ~ 6 Hz if GDS was controlled for in the correlations, but the other regions remained significant.

intervals containing significant correlations remained unchanged. This suggests that the task relevant peak in $-r_{AP}$ is a predictor of verbal memory performance, but it is more related to the subject's level of depression than to the other findings reported for in the phase-gradient measures.

There were no significant differences for phase synchrony between the SMC group and controls over the bands delta through to beta during the working memory task.

3.3. *Biophysical modeling*

Significant modeling results arose for scores derived from the eyes-closed resting condition. The SMC group had a smaller dendritic rate constant (α), which is equivalent to a prolonged dendritic response time ($p = 0.021$). The SMC group also showed reduced local cortical gain (G_{ei}, predominantly inhibitory in effect, $p = 0.023$) and reduced intrathalamic inhibitory gain (G_{srs}, $p = 0.003$), involving the thalamic reticular nucleus (TRN). For the SMC group, the intrathalamic inhibitory gain was also positively correlated with maze completion time ($r = 0.266$), and the rate of decline in errors with time ($r = 0.455$) and the rate of decline in maze over-runs with time ($r = 0.389$). This means that high intrathalamic gain was associated with low completion times and a faster decline in errors. Controlling for MMSE and GDS did not substantially change these correlations.

3.4. *Cognitive differences between groups*

The control group performed better than the SMC group over a range of cognitive tests. In the majority of cases, these were the same tests which were also significantly correlated with EEG power, phase-gradient or EEG model variables within the SMC group. For the word recognition task, significant group differences were observed for the verbal memory recall at trial 6 ($F = 5.098$, $p = 0.025$). When verbal memory performance was combined across the first four trials, giving an overall accuracy score, recognition performance was significantly superior in the control group ($F = 4.157$, $p = 0.043$). The SMC group showed deficits in speed across tasks. Specifically, the SMC group showed increased reaction time in the working memory task ($F = 8.55$, $p = 0.004$) and took longer to complete the maze task ($F = 4.210$, $p = 0.042$). The control group had a significantly greater decrease in the rate of maze errors with time ($F = 5.445$, $p = 0.021$) and the rate of maze overruns with time ($F = 5.263$, $p = 0.023$). Lastly, the SMC group showed a reduction in both forward (Control Mean = 6.18, SMC mean = 5.50) and reverse (Control Mean = 3.20, SMC mean = 2.85) digit span. However, this decline was only significant in the forwards condition ($F = 4.465$, $p = 0.036$).

4. Discussion

The majority of psychophysical effects found for the SMC group in this research are dissimilar to those of mild to severe AD. The SMC subjects had increased alpha power in both the EC and EO conditions, as well as increased beta power for EC. In the lower bands, the SMC group had increased EC theta frontally. The SMC subjects did not show decreased alpha desynchronization to the opening of the eyes. By contrast, AD subjects generally show a decrease of alpha and beta power, paralleled

by an increase in delta and theta power, compared with normative samples of elderly subjects [54–58, 7]. AD also produces a loss of EEG reactivity to eye opening [7]. The increased theta power demonstrated here for SMC is in accordance with the findings for AD. Cortical theta activity correlates with hippocampal atrophy, a finding consistent with the known neuropathology of AD [60].

The SMC subjects showed no differences in global phase synchrony in the bands delta through to beta, although preliminary longitudinal results from the SMC group suggest that there are changes in the global phase synchrony over time. A striking result of this study was the increase in spatio-temporal wave activity across all frequencies and times outside the event-related peak in $\sigma^2_{\mathrm{M}\Psi}$. This result was not confined to the working memory paradigm, but was also found for other experimental paradigms, for example, auditory oddball, facial emotion recognition and Go-Nogo (data not shown). When the specific spatio-temporal patterns were analyzed, the SMC subjects were shown to be less likely to engage in task-appropriate posterior to anterior spatio-temporal waves at the task-related peak in $\sigma^2_{\mathrm{M}\Psi}$ at 170 ms, $\sim$6 Hz for the working memory task. These findings are also in contrast to those for AD, where the most consistent results, in relation to EEG dynamics, have been a *decrease* in coherence [60–66] and global field synchronization [67] in the alpha and beta bands. These results for synchrony in AD have been interpreted in terms of functional disconnections among cortical regions (see Ref. 68 for a review).

The psychophysiological differences between SMC and elderly controls were related to a number of cognitive deficits in learning and executive functions. The EEG power increases in SMC were related to verbal learning deficits and longer maze learning time, while the model derived EEG scores were related to a number of indicators of poorer maze performance. The increased spatio-temporal wave activity in SMC was related to poorer working memory reaction time and the decreased posterior to anterior wave activity near the peak in $\sigma^2_{\mathrm{M}\Psi}$ was related to verbal learning deficits. In general, controling for MMSE scores or GDS did not substantially weaken these relationships and, in some cases, it strengthened them. This indicates that heterogeneity within the SMC group on global cognitive deterioration or sub-clinical depression was not inflating the correlations between psychophysical data and cognitive scores. The SMC group also performed more poorly than their matched controls on each of these cognitive tasks, reinforcing the finding that the changes in psychophysics do predict deficits in performance on some tasks.

Two major aspects of the findings from the current study suggest that changes in the EEG may be nonlinear across the SMC to the dementia continuum. Firstly, as already discussed, most of the EEG power differences are in the opposite direction to those found for comparisons between AD and controls. The findings involving phase-synchrony and phase-gradients also deviate from those findings using similar measures on AD subjects. Secondly, and most intriguing, are the positive correlations of EO alpha band power and spatio-temporal wave activity with reverse digit span. These findings show that psychophysical changes in SMC that are related to poor

performance on some tasks, predict good performance on one relatively difficult task involving working memory.

The EEG model revealed abnormal activity in the SMC group for populations of local cortical and thalamic neurons. The localized activation of neocortical cells is thought to occur in part due to thalamo-cortical (TC) activation of fast-spiking (FS) cortical inhibitory interneurons within minicolumns [69, 70]. It has been suggested that these FS interneurons are involved in the rapid control of neural activity in intracortical networks [71], regulating sensory-evoked activity via feed-forward inhibitory mechanisms [69]. These abnormalities in the SMC group may reflect reduced activation of FS cortical inhibitory neurons, and abnormal modulation of TC projections by the inhibitory TRN. These changes may reflect a break-down in the mechanisms involved in cortical regulation. The intrathalamic inhibitory gain involving the TRN was also found to be associated with maze completion time. This suggests that abnormal intrathalamic activity may interfere with efficient information processing, resulting in slower performance on the Maze task.

In addition, in the EEG model, it shows that increased gain of inhibitory neurons of the TRN can reduce TC activity and the resulting alpha power, whereas decreased gain of the TRN will increase alpha power [33, 36]. Therefore, the decreased gain of the intrathalamic network involving the TRN as found with SMC is consistent with the observed increase in alpha power, which may also reflect interference in efficient information processing.

The decrease of inhibitory gains in cortex and thalamic circuits may also point to the genesis of the increase in spatio-temporal waves seen in SMC. TC interactions have previously been hypothesized to play a critical role in the changes in spatio-temporal wave activity seen in AD patients in the gamma band [12]. Loss of cortical and thalamic inhibition, combined with the interplay of TC feedback circuits, may play a critical role in the generation of excess waves in inappropriate contexts. The direction of the effect (increased global waves) and nature of the population (SMC) rule out the loss of cortico-cortical connectivity as a likely cause.

Several lines of evidence support the hypothesis that the psychophysiological changes in SMC found in this study may indicate an initial compensatory processing to the early cognitive decline. This hypothesis has previously been put forward to explain contradictory results in relation to synchrony measures in pre-senile subjects [7]. A similar effect is found in fMRI studies, where there is increased task activation in subjects at risk for developing AD, and decreased activation in advanced AD [72]. At the level of neurochemistry, a reduction of cholinergic activity is implicated in AD, particularly at the latter stages, but the number of cholinergic terminals is either unchanged or increased in MCI [71–73]. From the present study, we add the converging evidence of increased alpha band power and increased spatio-temporal wave activity in SMC subjects. The positive correlation of these measures with reverse digit span provides the strongest hint that these changes may be compensatory.

The working hypotheses initiating the present research were only partly borne out in the results. There are verbal memory deficits in SMC and also deficits in other memory-related cognitive tasks such as maze performance, digit span and the visual working memory task. Each of these cognitive deficits was correlated to one or a number of the EEG-derived measures within the SMC group. These correlations varied in strength from weak ($r = 0.2$) to moderate ($r = 0.44$), and were not, in general, attributable to heterogeneity within the SMC group on global cognitive functioning (MMSE) or sub-clinical depression (GDS). The strongest correlations were between eyes-open alpha power at peak alpha frequency and verbal recall scores. The EEG-derived measures used in this study were those that showed significant differences between the SMC and the control groups. Contrary to results for AD, the SMC group showed increased alpha power, no changes in global synchrony, and an increase in spatio-temporal wave activity. Yet, the direction of the between groups differences was predictive of several cognitive deficits in the SMC group; i.e., increased alpha power and increased spatio-temporal activity were in general associated with poorer memory-related performance. The results of this study suggest a nonlinear set of relationships between EEG measures and memory-related cognition across the SMC to the dementia continuum. Future research into early-stage progression of dementia will integrate Magnetic Resonance Imaging gray matter loss, Genetics (including ApoE), and the current neuropsychological/EEG/ERP scores from the Brain Resource International Database.

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