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C145 as a short-latency electrophysiological index of cognitive compensation in Alzheimer's disease

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Abstract

Brain plasticity and cognitive compensation in the elderly are of increasing interest, and Alzheimer's disease (AD) offers an opportunity to elucidate how the brain may overcome damage. We provide neurophysiological evidence of a short-latency ERP component (C145) linked to stimulus relevancy that may reflect cognitive compensation in early-stage Alzheimer's disease (AD). Thirty-six subjects with early-stage, mild AD and 36 like-aged normal elderly (Controls) had their EEG recorded while performing our Number-Letter task, a cognitive/perceptual paradigm that manipulates stimulus relevancies. ERP components, including C145, were extracted from ERPs using Principal Components Analysis. C145 amplitudes and spatial distributions were compared among Controls, AD subjects with high performance on the Number-Letter task, and AD subjects with low performance. Compared to AD subjects, Control subjects showed enhanced C145 processing of visual stimuli in the occipital region where differential processing of relevant stimuli occurred. AD high performers recruited central brain areas in processing task relevancy. Controls and AD low performers did not show a significant task relevancy effect in these areas. We conclude that short-latency ERP components can detect electrophysiological differences in early-stage AD that reflect altered cognition. Differences in C145 amplitudes between AD and normal elderly groups regarding brain locations and types of task effects suggest compensatory mechanisms can occur in the AD brain to overcome loss of normal functionality, and this early compensation may have a profound effect on the cognitive efficiency of AD individuals.

Keywords

Event-Related Potentials (ERP); Electrophysiology; Alzheimer's disease (AD); EEG; Principal Components Analysis (PCA); Short-latency ERP component; Compensatory mechanisms; Brain plasticity; C145

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Introduction

Brain plasticity and cognitive compensation in the elderly are of immense interest, particularly concerning Alzheimer's disease (AD). Some individuals with AD have higher cognitive efficiency than others despite a relatively similar level of functional impairment, and how the brain overcomes damage may explain how these individuals maintain good cognitive performance. AD may functionally be expected to reduce the neural activity in the damaged brain regions. Increasing neural activity in other brain regions might allow some AD individuals to compensate and thus perform perceptual-cognitive tasks with accuracy more like that of normal, healthy elderly Control subjects. Better understanding of the biological bases of how some individuals with AD compensate for loss of neurological functionality could lead to improved clinical assessment and more targeted therapeutic approaches. This would be of paramount importance to patients struggling with early stage dementia as it might improve their daily functioning.

Both reduction of some kinds of neural activity and increases in other kinds can be detected non-invasively with MEG and EEG [1, 2], which provide the high temporal resolution required to identify neurological mechanisms involved early in the information processing stream. In particular, brain Event-Related Potentials (ERPs) [3, 4] and their underlying components can measure electrophysiological responses to perceptual and cognitive tasks and show promise as biomarkers that can detect and predict AD [5-13].

However, much of the research has focused on long-latency post-stimulus ERP components that represent later cognitive processes affected by AD, including memory and executive functioning. Well-known ERP components, such as P300, N400, and P600, have been implicated in the cognitive decline associated with AD [12, 14, 15]. The impact of AD on ERPs is consonant with the general belief that memory and reasoning are among the first cognitive activities damaged by the disease. Short-latency ERP components that precede P300, such as P100 and N100, are considered to be exogenous sensory components or representative of early visual stimulus processing [8, 9, 16]. The sequence of neural functions between early sensory processes and executive processes (P300 and beyond) is not well defined, and evidence suggests AD may profoundly affect ERP components in this time region. These ERP components, such as N200, P200, and C250 can, dependent on the perceptual-cognitive paradigm, be modulated by task relevancy effects [17-19], and AD has been shown to affect both latency and amplitude measures [5, 6, 10, 20]. Although the cognitive characteristics of short-latency ERP components have been reported in research with normal subjects [21-23], there is little consensus on their utility in differentiating AD from normal aging [9, 12].

Such utility might depend upon several key aspects. The tasks used to elicit ERP components are essential in linking observable behavior with neurological mechanisms. Our Number-Letter task [5, 6, 24] manipulates working memory, stimulus expectancies, and demands on executive functions, among other cognitive processes. This provides the opportunity to measure ERPs under a variety of conditions so that the corresponding underlying ERP components can be differentially affected and thus be analytically separable. In addition, untangling and identifying the underlying components of ERPs is crucial when attempting to determine the timing of brain activity related to a particular cognitive process. Multivariate analysis, such as Principal Components Analysis (PCA), provides a formal, rigorous method of identifying ERP components [25]. Other measurement methods may be more influenced by arbitrary assumptions, such as selecting latency regions and measuring the maxima or minima of waveforms as though no components overlap in time. It is possible that discriminative utility in short-latency ERP

components has not been found because of inadequate tasks or component measurement methods.

This paper utilizes C145, a short-latency ERP component with its maximum at 145 ms post-stimulus, to investigate the electrophysiological underpinnings of cognitive compensation in early-stage AD. We will use the behavioral and electrophysiological characteristics of normal elderly as a baseline for comparison in studying compensation, which is operationally defined here as AD individuals showing different patterns of brain activity linked to more “normal” cognitive behavior than their impaired peers. A compensatory mechanism should appear differently in those AD individuals with better behavioral performance. ERP component C145 reflects early differential processing of task-relevant and task-irrelevant stimuli, and we will show spatially and functionally different patterns of brain activity among normal elderly, cognitively high-performing AD subjects, and cognitively low-performing AD subjects. Understanding the neurological bases of physiological and pathological brain aging is vital, and we demonstrate that these patterns of C145 activity may represent how the brain begins to overcome damage caused by AD.

Materials and Methods

Study Subjects

We used 36 elderly individuals diagnosed with early-stage Alzheimer's disease (AD) and 36 like-aged elderly Controls (Table 1), totaling 72. These subjects were recruited from the Memory Disorder Clinic at the University of Rochester and other affiliated University of Rochester clinics. All AD subjects were evaluated by memory-disorder physicians and met standard criteria for AD (NINCDS-ADRDA) [26] and DSM-4TR criteria for Dementia of the Alzheimer's Type [27] and were considered early in the course of the disease. This study was conducted prior to the acceptance of new research diagnostic criteria for AD and no CSF or imaging biomarkers were available. The memory-disorders physicians, who were blind to our study data, based their assessments on the patient history, relevant laboratory findings, neuropsychological testing, and imaging studies routinely performed as part of comprehensive clinical assessment of dementia. Control subjects were cognitively normal for their age and demographically similar to the AD participants. Most Control participants were selected from the same Memory Disorder Clinic and underwent the same clinical assessment for cognitive impairment. Some Control participants were volunteers from the community but were evaluated with a comprehensive neuropsychological test battery designed to indicate memory impairment.

The gender, age, education, and Mini-Mental State Examination (MMSE) [28] demographics for each group were relatively well-matched (Table 1). There were no significant group or gender differences for age and education between the AD and Control groups. There was of course a significant group effect ($F(1,71) = 94.47$, $p < 0.0001$) for MMSE score. Thirty-four of the 36 subjects in the AD group were taking cholinesterase inhibitors to treat mild AD (one man and one woman were not). One man in the Control group was taking a cholinesterase inhibitor prescribed by his primary care physician. The study sample utilized in this research is one of convenience derived from clinical sources and thus situations such as this are possible even if the subject met strict criteria as a Control.

Exclusion criteria for both groups included clinical (or imaging) evidence of stroke, Parkinson's disease, HIV/AIDS, and reversible dementias, as well as treatment with benzodiazepines, antipsychotic, or antiepileptic medications. As an additional inclusion criterion, all subjects had a previous clinically administered score of 19 or higher on the MMSE (out of 30, where a higher score indicates greater cognitive functioning). Our study

received IRB approval from the University of Rochester Research Subjects Review Board, and informed consent was obtained from each subject.

The Number-Letter Paradigm

The Number-Letter task [5, 6, 24] manipulates working memory, stimulus relevancies and expectancies, and demands on executive functions. This provides the opportunity to measure ERPs under a variety of independent conditions so that the corresponding underlying ERP components can be separated. Previous research with this task has shown it to manipulate many common and useful ERP components, including P300 [5, 29], Contingent Negative Variation (CNV) [5, 24], the C250 "memory storage" component [5, 17], C145, and other short- and long-latency ERP components.

Two numbers and two letters were flashed individually in random order at intervals of 750 ms with this sequence of four stimuli preceded and followed by a filled square comparable in size to the numbers and letters. All visual stimuli were large (height of 5.3° visual angle), white (55 cd/m^2), and presented briefly (~20 ms) on a dark background. On a number-relevant block of trials, the participant compared the two numbers in each trial for numerical order, the letters being irrelevant to the task. On another block of trials, the numbers were irrelevant and the task involved comparing the two letters for alphabetic order. At the end of each trial, the participant said "Forward", "Backward", or "Same" to indicate the order of the two relevant stimuli. The numbers (1 to 6) and letters (A to F) were randomly chosen with replacement, and the sequences of numbers and letters in the four temporal intratrial positions were randomized (constraint of two numbers and two letters per trial). Every participant was shown a randomized sequence of trials. One block of 102 number-relevant and one block of 102 letter-relevant trials were completed by each subject in random order. Subjects were provided practice trials before these experimental blocks began. Successful performance required discriminating between stimuli relevant and irrelevant to the task. Memory storage of the first relevant stimulus was required in order to compare it with the second relevant stimulus.

Subject performance on the Number-Letter Task

All subjects were capable of performing the Number-Letter task. On average, the AD group correctly answered 87% of the trials and the Control group answered 98% of the trials (Table 1). The Control group significantly outperformed the AD group ($F(1,71) = 38.68$, $p < 0.0001$). No main gender effect or group by gender interaction occurred on Number-Letter task performance. While there was a significant within-subjects task effect ($F(1,71) = 7.80$, $p < 0.01$) such that for all subjects the letter-relevant task was more difficult, there was no task by group or task by gender interaction. The letter-relevant task was therefore equally difficult for the AD and Control groups.

To examine possible compensatory mechanisms within the AD group, we divided AD subjects on the basis of their Number-Letter task performance. This was done to link our electrophysiological responses directly with resultant behavior, whereas basing "high performance" through other means, such as neuropsychological tests, would not yield such an explicit relationship to our measured underlying brain activity. Those AD subjects with 90% or greater accuracy were placed in the AD high performance (AD-high) group, and those with less than 90% accuracy were placed in the AD low performance (AD-low) group (Table 1). This was done to divide the AD group fairly evenly near the AD group performance average of 87%. There was no significant subgroup effect for age, education, and severity of dementia (as measured by the MMSE), suggesting the AD-high and AD-low groups were demographically well-matched, and cognitively they were equally impacted by AD. There was also no significant difference between subgroups on the Geriatric Depression

Scale (GDS) [30], indicating the two subgroups were equally and mildly impacted by depression (AD-high mean (SD): 6.7 (4.8); AD-low: 6.9 (4.5)). Predictably (since the subgroups were divided by accuracy) there was a significant subgroup effect on accuracy ($F(1,35) = 64.88$, $p < 0.0001$). We also found a gender effect ($F(1,35) = 5.59$, $p < 0.05$) such that AD men slightly outperformed AD women, but there was no subgroup by gender interaction, suggesting this gender disparity was independent of performance group placement.

EEG Recording

Scalp electrodes (a subset of the 10/20 electrodes including O1, O2, OZ, T3, T4, T5, T6, P3, P4, PZ, C3, C4, CZ, F3, F4, and EOG with reference to linked earlobes) recorded electrical brain activity while the participant performed the Number-Letter task. Frequency bandpass of the Grass amplifiers was 0.1 to 100 Hz. Beginning 30 ms before each stimulus presentation, 155 digital samples were obtained at 5 ms intervals. Subsequently, the digital data were digitally filtered to pass frequencies below 60 Hz, and artifact criteria were applied to the CZ and EOG channels to exclude those 750 ms epochs whose voltage range exceeded 200 μV or whose baseline exceeded ±250 μV from DC level (baseline was mean of 30 ms pre-stimulus). The ERPs were based on correct trials and data not rejected for artifacts. Mean artifact rejection rate for all subjects was 11.0% (SD = 18.5%).

Event-related Potential Components: Principal Components Analysis

We derived ERPs for each subject from their EEG vectors (155 time points) by averaging each vector separately for each of the 16 task conditions in this experimental design. Kayser and Tenke [31] discuss the difficulty in visually identifying and quantifying the ERP components “even after thorough inspection of the waveforms”. Because the ERP itself is a multivariate observation (due to its many post-stimulus time samples), we applied a multivariate measurement method, Principal Components Analysis (PCA) [4, 25, 31, 32], to identify and measure the latent components of the ERPs. Volume conduction in the brain suggests an additive ERP model, which underlies the PCA process in extracting the component structure [25]. PCA provides a parsimonious measurement system that relies on the implicit structure of the data in developing composite measures of brain activity. PCA forms weighted linear combinations of the original measurements that capture most of the relevant variance and allows temporal or spatial overlap of components that are orthogonal. Our approach to PCA uses ERP time points as the variables and subjects and task conditions as cases. This allows the computation of component scores for each of these cases.

We previously performed the PCA on ERPs measured at CZ using a correlation matrix of the 155 time points on a group of 48 individuals: 12 with clinically diagnosed AD, 12 individuals with Mild Cognitive Impairment (MCI), 12 elderly Controls, and 12 young subjects [5]. This set of varying groups all completed the same Number-Letter task under the same experimental and recording conditions, and these subjects and their ERP data (1728 ERPs used in the PCA) were used in this previous study to discriminate between AD and normal cognition using ERP component scores. This set of subjects was used to create components that would be more generalizable to a wider array of individuals [33]. Deriving a component solution from a narrow set of similar individuals has been shown to limit the range in the variables and attenuate correlations among variables that can result in falsely low estimates of component loadings [34].

Eight temporal ERP components were retained by Kaiser's Eigenvalue > 1 rule (accounting for 95% of the variance). These included well-known components, such as C415, which is sometimes called parietally-loaded P300 [15, 17, 29, 35-38], CNV [39], “memory storage” component C250 [17, 36], and C145, and other short- and long-latency components. Part of

the PCA output (the component loadings) represented the temporal waveforms of each ERP component [5]. Due to volume conduction, the central midline location (CZ) includes a composite of the brain activity from surrounding areas. Therefore, it is reasonable to apply the component structure derived at CZ to other electrode sites. Beginning with ERPs for each electrode, the scoring procedure mathematically measured ERP component scores for each of the components for each electrode. The SAS 9.1.3 procedures FACTOR and SCORE were used to generate the component solution and calculate the ERP measures [40].

The component scores for the C145 component (maximum at 145 ms post-stimulus) were retained for further analysis. We focus on C145 here in order to assess brain functions that are early post-stimulus in the information processing stream. Also our prior results found C145 measures at electrode CZ were helpful in discriminating AD individuals from Controls [5]. There were ERP component scores for 16 task conditions: two stimulus relevancies (relevant, irrelevant), four intratrial positions (referred to as part), and two stimulus types (numbers, letters). To visually compare spatial brain patterns, we averaged the C145 ERP component scores at each electrode for each subject group (collapsing over stimulus types and parts). We then plotted these average measures as topographical maps using the Bioelectromagnestism Toolbox [41] in MATLAB R2007b [42].

C145 Scores for Occipital and Central Regions

For mean difference significance tests, we used the occipital region (average of electrodes O1, OZ, and O2) because it showed through inspection of topographical maps the largest amplitude difference between Control and AD groups as well as a relevancy effect for the Control group. To measure possible compensation in the AD group, we selected the central region (average of electrodes C3, CZ, and C4) though there were others in more anterior brain regions that also showed a relevancy effect. Mean activity at central electrodes was not significantly correlated with that at the occipital region for all 72 subjects (both AD and Control) (for the relevant condition, r = 0.01, n = 72, $p = 0.95$; for the irrelevant condition, r = 0.06, n = 72, $p = 0.60$). We also focused on the central region because the frontal region tended to reflect muscle movement and artifacts and this noise interfered with obtaining significant task effects.

Averaging across the region of occipital electrodes was appropriate because there were no significant interactions between either task relevancy or stimulus type and occipital electrode site (O1, OZ, O2) for the Control (task relevancy: $F(1,35) = 0.40$, $p = 0.67$; stimulus type: $F(1,35) = 0.50$, $p = 0.60$) or AD (task relevancy: $F(1,35) = 0.01$, $p = 0.99$; stimulus type: $F(1,35) = 0.11$, $p = 0.90$) groups. Similarly, there were no interactions for the Control (task relevancy: $F(1,35) = 0.02$, $p = 0.98$; stimulus type: $F(1,35) = 0.91$, $p = 0.40$) or AD (task relevancy: $F(1,35) = 0.07$, $p = 0.94$; stimulus type: $F(1,35) = 0.05$, $p = 0.95$) groups in the central region (C3, CZ, C4).

Additionally, for all groups combined, C145 components scores did not significantly correlate with P300 component scores (measured through PCA; see Chapman et al., 2007 for more information) in the occipital region (for the relevant condition, r = 0.11, n = 72, $p = 0.34$; for the irrelevant condition, r = 0.08, n = 72, $p = 0.51$) or in the central region (for the relevant condition, r = -0.08 n = 72, $p = 0.53$; for the irrelevant condition, r = -0.10, n = 72, $p = 0.42$). This indicates that C145 represents different neurophysiological activity than ERP component P300, which has been studied with respect to AD and cognitive compensation.

Statistical Comparisons

To compare task effects within groups, we used mixed design ANOVA with repeated measures. To compare C145 component scores between groups, we used one-way ANOVA.

We used PCA to yield component scores that are based on a weighted combination of time points, which avoids multiple testing of measures at different time points. Demographic effects were analyzed between groups using two-way ANOVA. We performed all ANOVA procedures in SAS using PROC GLM. Pearson correlation coefficients were also computed in SAS using PROC CORR.

Results

The Number-Letter task produced a set of ERP components related to various conditions within the paradigm. We measured these ERP components under two simultaneous but dissociated task conditions: stimulus type (if the stimulus was a number or a letter) and stimulus relevancy (if the stimulus was relevant or irrelevant to completing the task).

ERP Component C145

C145, a short-latency ERP component with a maximum at 145 ms post-stimulus, was among the ERP components extracted by PCA [5] (Fig. 1). This component was useful in discriminating individuals with AD from like-aged normal elderly [5]. Short-latency ERP components, such as N100, P100, N200, P200, and PNwm, may be measured during time zones that include 145 ms post-stimulus [12, 43-45]. However, it is difficult to compare ERP components formally measured with a rigorous multivariate approach such as PCA with those that were developed without such an approach. Research has indicated these short-latency components can reflect differential processing of target and non-target stimuli [23]. Chapman [21] previously measured ERPs at a short-latency of 105 ms post-stimulus in young adults that showed a task relevancy effect.

Task Effects in the Occipital Region

Examination of C145 spatial brain patterns (Fig. 2) revealed its largest activity (negative) occurring in the occipital region in Controls. Compared to the Control group, mean AD component scores in the occipital region were roughly one-third the amplitude ($F(1,71) = 12.99$, $p < 0.001$) (Fig. 1). For the Controls, there was a significant difference between C145 under relevant and irrelevant stimulus conditions ($F(1,35) = 4.27$, $p < 0.05$) in the occipital region. AD subjects' mean C145 waveforms for relevant and irrelevant stimuli showed no difference at the occipital region ($F(1,35) = 0.18$, $p = 0.67$).

In addition to the task relevancy effect, the Control group showed a stimulus type (number, letters) effect ($F(1,35) = 5.92$, $p < 0.05$). The AD group also had this effect in the occipital region ($F(1,35) = 8.95$, $p < 0.01$).

Task Effects in the Central Region

We examined the spatial pattern of C145 difference scores between task relevancy conditions to determine if AD subjects process relevant stimuli differently from irrelevant stimuli in another brain area (Fig. 2). At the central region, AD subjects showed a significantly increased positive response to relevant compared with irrelevant stimuli ($F(1,35) = 8.70$, $p < 0.01$) that the Control group did not show ($F(1,35) = 0.34$, $p = 0.56$). Both the Control ($F(1,35) = 11.89$, $p < 0.01$) and AD ($F(1,35) = 10.06$, $p < 0.01$) groups showed a significant stimulus type effect.

C145 as an Index of Compensation

To examine possible compensatory mechanisms among the AD subjects, we divided the AD group into two subgroups based on a cut-off of 90% performance accuracy on the Number-Letter task: a high performance group (AD-high) and a low performance group (AD-low) (Table 1). Examining C145 amplitudes (Fig. 3) revealed a striking difference between the

AD-high and AD-low groups. First, the AD-low group showed essentially zero differential processing of relevant and irrelevant stimuli across the brain. The AD-high group, conversely, committed a large proportion of neural resources to task relevancy processing. The largest differences between relevant and irrelevant stimuli occurred in central and frontal regions.

A compensatory mechanism linked to better performance in AD should appear larger in the AD-high group than in the Control group or the AD-low group (Fig. 4). At this early stage of post-stimulus processing, C145 amplitude scores showed Control subjects processed task relevancy in the occipital region such that they demonstrated a larger (more negative) response to relevant than irrelevant stimuli. Neither the AD-high nor the AD-low group showed a task relevancy effect in the occipital region. The AD-high group had an overall increased negative response compared to the AD-low group ($F(1,35) = 4.26$, $p < 0.05$), though this response did not differ between task relevancies.

At the central region, however, the AD-high group performed early processing of task relevancy with a statistically significant difference between relevant and irrelevant stimuli ($F(1,18) = 8.97$, $p < 0.01$). This location lacked significant task relevancy processing in normal elderly. More importantly, there was no significant relevancy effect at central regions for the AD-low group. This suggests that AD individuals who performed the Number-Letter task with greater accuracy (i.e., demonstrated cognitive performance closer to that of normal elderly) recruited additional brain resources in short-latency stimulus relevancy processing.

Furthermore, correlations between Number-Letter task accuracy and C145 component scores for task relevancy indicate that this electrophysiological measure was related to task behavior and that compensation in central regions contributed to better task performance (Table 2). When subjects from all three groups (Control, AD-high, and AD-low) were included, C145 amplitudes in the occipital region for relevant ($r = -0.42$, $p < 0.001$) and irrelevant stimuli ($r = -0.43$, $p < 0.001$) were significantly negatively correlated with accuracy but not in the central region . Importantly, considering only the AD subgroups, the difference between C145 relevant and irrelevant amplitudes in the central region correlated positively with performance ($r = 0.34$, $p < 0.05$).

Discussion

This paper reports several important results concerning early post-stimulus processing in normal aging and AD. First, C145 revealed a task relevancy effect manifested differently in normal elderly and AD groups such that the normal Control group showed the largest effect in the occipital brain region while the AD group showed more anterior involvement in the early post-stimulus processing of stimuli. Second, dividing the AD group into subgroups by performance accuracy on the Number-Letter task indicated that the AD subgroup who achieved higher accuracy may be compensating by recruiting additional central brain areas to process task relevancy.

Examining task relevancy effects has been useful in developing ERP markers for AD [5, 6]. For the Controls, there was a significant difference between C145 under relevant and irrelevant task conditions in occipital regions. AD subjects' mean C145 waveforms for relevant and irrelevant stimuli show no difference in the occipital region. It should be noted that the raw ERP waveform recorded at OZ (Fig. 1) appears to show a difference between task relevancies in the AD group; however, this difference was due to other ERP components that *overlap* with C145 (especially CNV [5], which relates to stimulus expectancies). We used differing experimental conditions that manipulate varying

components, including CNV, in conjunction with PCA to untangle overlapping components [25].

In the central region, the AD group as a whole showed a significant task relevancy effect whereas the Control group showed no relevancy effect. This suggests an interesting idea about brain plasticity that is contrary to the general and perhaps outdated view that AD causes diminished brain activity. Our results agree with Transcranial Magnetic Stimulation (TMS) findings [46] in that in early-stage AD hyperexcitability in the brain may lead to functional compensation. The AD group demonstrated a different spatial pattern of brain activity for this short-latency component. Even at this early stage of post-stimulus processing, there were remarkable differences between individuals with mild AD and normal elderly. This mirrors previous findings that AD does not always result in smaller component score amplitudes [5, 6] and that neuronal loss may be compensated through reorganizing neural circuits [46].

Compensatory mechanisms may maintain or restore behavior when underlying neurological mechanisms are damaged or less efficient [18, 19, 23, 47-50]. Dividing the AD group into two subgroups based on their performance on the Number-Letter task (Table 1) indicated that those AD individuals capable of achieving more accurate performance may process early post-stimulus relevancy differently than those AD subjects who have lower performance (Fig. 3). The difference in task relevancy processing between the AD-high and AD-low group was striking, where the AD-low group showed essentially no early processing of task relevancy while the AD-high group recruited more neural resources, particularly at anterior locations.

Examining task effects between the occipital region and the central region revealed where and to what extent each group performed task relevancy and stimulus type processing (Fig. 4). The Control group had a significant task relevancy effect in the occipital region that neither the AD-high nor the AD-low group showed. Also, the occipital region showed an interesting processing trend. C145 amplitudes in the occipital region became smaller from Control to AD-high to AD-low groups. AD subjects failed to differentially process relevant and irrelevant stimuli; however, the AD-high performance group showed an overall larger occipital response, one that more closely matched that of Controls, than the AD-low group.

At central areas (Fig. 4), the amplitudes for the Control, AD-high, and AD-low groups were more similar to each other than in the occipital region. All three groups presented a significant stimulus type effect (numbers, letters). However, the AD-high subgroup was the only group to present a significant task relevancy effect (relevant, irrelevant). It seems, therefore, that the AD-high group recruited additional more anterior neural resources to perform early identification of relevant stimuli.

We examined the correlational links between Number-Letter task performance and C145 amplitudes under task conditions (Table 2). Indeed, we found C145 amplitudes for relevant and irrelevant conditions in the occipital region were significantly negatively correlated with accuracy, indicating larger negative amplitudes positively impacted resultant performance. Including the Control group in a correlation analysis for the central region was not logical given the hypothesis that this region was involved in compensation due to disease impairment. Therefore, we studied the correlation between C145 amplitudes and accuracy using only the AD subjects and found a significant positive correlation ($r = 0.34$) between accuracy and C145 amplitude difference scores (relevant – irrelevant). It was the differential processing at the central region that improved some AD subjects' performance. Also, there was a negative correlation ($r = -0.28$) between C145 irrelevant scores in the central region and accuracy, implying that perhaps the AD-low subgroup focuses to a larger extent on

irrelevant stimuli than the AD-high subgroup, which might have in turn negatively impacted the AD-low group's ability to complete the task successfully.

These results suggest that the AD-high group achieved better performance through a combination of larger, more Control-like activity in occipital areas and compensation through recruiting more anterior areas in processing task relevancy. Clément and Belleville [51] found support for such a hypothesis using fMRI and word-pair recognition tasks in cognitively high-performing and low-performing groups of subjects with Mild Cognitive Impairment (MCI). We suggest the deficits of AD cannot simply be explained as a reduction of activity in key neurological areas. Compensation, also, is not simply involvement of additional brain areas. How these additional areas are used in early information processing as related to task dimensions (e.g., stimulus type for AD-low, relevancy for AD-high) is crucial to compensating for AD-related impairment.

Although the AD-low group did not show a task relevancy effect for this short-latency component, they did demonstrate a stimulus type effect (differentiating between numbers and letters) at both the occipital and central regions (Fig. 4). This indicates the AD-low group was processing some aspect of the Number-Letter task at this early stage, even if it was not differentiating between relevant and irrelevant stimuli. It is possible the AD-low group was only processing stimulus type but not adequately identifying whether the numbers or letters were relevant to task, which was crucial to successful performance.

Our results could perhaps be explained by the AD-low group simply being further advanced in the disease than the AD-high group, which would account for their poorer performance on the Number-Letter task. We do not have sufficient biomarker or imaging data that would allow us to differentiate the degree of neurodegeneration between the two groups. However, there was no significant difference in Mini-Mental State Examination score [28] between the AD-high and AD-low groups, indicating the severity of dementia was comparable (Table 1). Furthermore, these subjects were all clinically diagnosed with early-stage AD by memory-disorder physicians. It is also possible that the individuals in the AD-high group would have outperformed the individuals in the AD-low group regardless of the disease. Education speaks to this issue, and the two AD subgroups were similar in this regard. The AD subgroups also showed comparable intelligence as measured by the American National Adult Reading Test (AMNART) [52] ($F(1,35) = 2.36$, $p = 0.13$). Finally, comorbid depression can affect cognitive ability, but testing with the GDS [30] showed no significant difference between the AD-high and AD-low subgroups ($F(1,35) = 0.03$, $p = .86$).

It should be noted that C145 is a very short-latency ERP component for the visual system, with other components that follow it also impacted by AD [5, 7, 10, 13-15]. It is not reasonable to assume compensation observed during this early component completely explains Number-Letter task performance, nor is it reasonable to state that the AD-low subgroup fails entirely to discriminate between stimuli relevant to the task and those that were not. It was remarkable, however, that this early, short-latency component did have such a strong influence on cognitive performance for this task (as seen by the significant correlations between C145 amplitudes and accuracy). How the AD-high group achieves higher performance must be furthered studied with subsequent ERP components; this report establishes that this pattern of short-latency brain activity differentiates between AD subjects who maintain better cognitive performance from those who do not. Further work to examine C145 task effects in individuals with MCI (some of whom later develop AD) might also elucidate when and where AD-related damage begins to impact early information processing.

Compensatory mechanisms that maintain function have been described in AD for non-cognitive tasks, including motor function [46, 53]. Babiloni et al. [53] studied desynchronization/synchronization of alpha and beta electroencephalographic (EEG) rhythms related to finger movements and found some different topographic features in mild AD patients not found in normal old subjects. Ferreri et al. [46] used different techniques for studying compensatory mechanisms in motor function. Cortical motor output to upper limbs was elicited by TMS, and mild AD patients showed increased motor cortex excitability that indicated a frontal and medial shift in excitable scalp sites compared with Controls. Their findings fit nicely with the frontal shift of EEG rhythms in early AD patients [53] as well as with our frontal shift of ERP measures of C145 in early AD reported here, although they did not occur in precisely the same brain locations.

In addition, others have discussed compensatory mechanisms in aging and AD related to cognitive tasks [19, 23, 50, 51, 54-56]. Riis et al. [23] examined compensation in normal elderly and young adults and found that a longer-latency ERP component (P300) indexed appropriation of greater neural resources. They found significant stimulus effects in short-latency components, but these effects did not modulate among their groups. We have found with the Number-Letter paradigm that task effects that relate to performance do occur differently between AD and Control subjects in a short-latency component. fMRI studies have indicated AD and pre-clinical AD subjects recruit more anterior brain areas, including parietal and temporal areas, to successfully complete cognitive tasks, including memory encoding and retrieval [51, 54, 56-59]. EEG and ERPs provide much higher temporal resolution than fMRI, PET, and other neuroimaging techniques and thus allow examination of short-latency neural activity that may represent task-related cognitive processing before memory encoding occurs.

Many studies of compensation in AD focus on higher-level, longer-latency cognitive aspects. Our results suggest that compensation may begin very early in the information processing stream (145 ms post-stimulus), and this may help explain why some individuals with AD have greater cognitive efficiency than others, even if they present the same level of cognitive impairment through clinical assessment. While this study focused on group differences to elucidate possible compensation, C145 has been shown to be useful in identifying AD individuals [5] and with further study could possibly suggest further means to measure compensatory activity at the individual level. Studying C145 and other ERP components related to compensation might reveal basic anatomical and functional differences that are blurred at the level of behavioral analysis which could yield improved methods to diagnose and predict individual clinical outcomes. If researchers grasp a better understanding of brain plasticity and how the brain compensates for the damage caused by AD, it may lead to more timely and efficient treatments.

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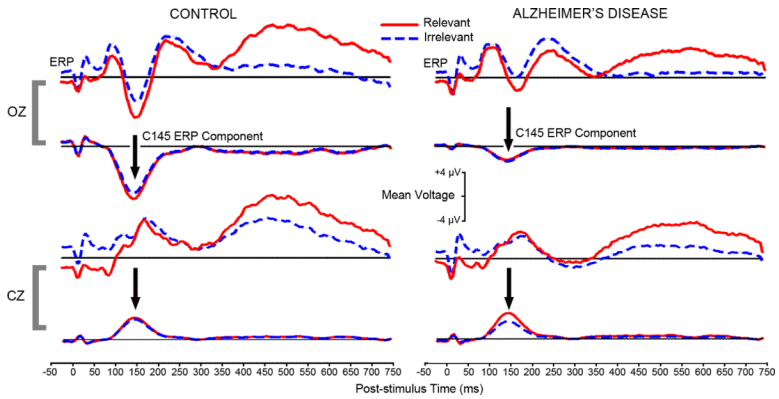

Figure 1.

Average ERPs and C145 waveforms for relevant and irrelevant task conditions in the Number-Letter task for AD and Control groups. These waveforms are shown for midline scalp sites OZ and CZ from the International 10-20 System (averaged over stimulus type and intratrial part variations). Either numbers or letters were assigned to be relevant to completing the task on different blocks of trials. In these C145 component waveforms (measured with PCA), the voltage metric has been restored by multiplying the loading at each time point by the standard deviation of the data set at the corresponding time point [5, 25]. We adjusted the C145 waveform amplitudes at all time points by the mean C145 component score for each group and each relevancy condition.

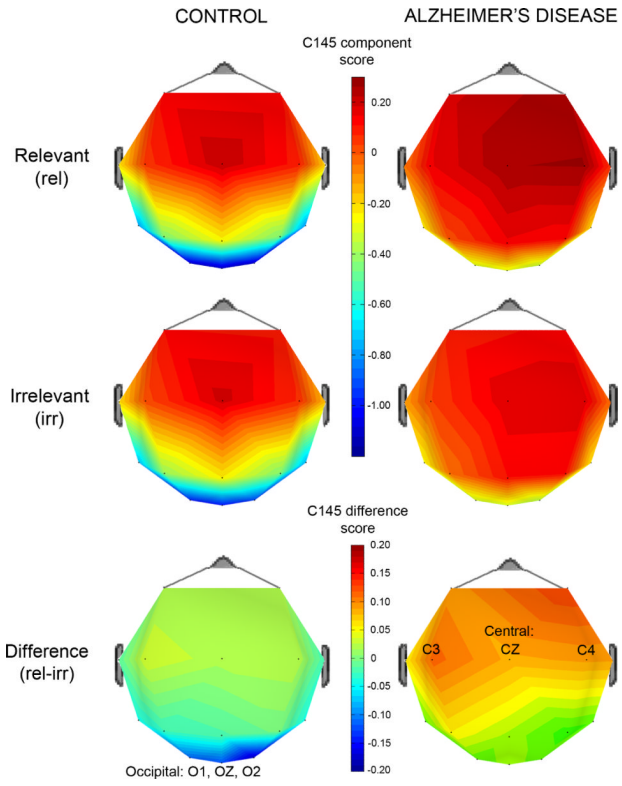

Figure 2.

Distinct topographical patterns of C145 amplitudes (PCA component scores) for AD and Control groups for differential neural processing of task relevant stimuli. We averaged C145 component scores over stimulus type and intratrial part variations. Either numbers or letters were assigned to be relevant to completing the task on different blocks of trials. C145 difference scores (rel – irr) measure the relevancy effect with other effects removed (e.g., individual differences, physical stimulus differences, stimulus category differences). The spatial distribution (based on the International 10-20 System) of difference scores indicates where the differences between C145 amplitudes for processing relevant and irrelevant stimuli are larger for each group. For the Control group, the largest differences for task relevancy occurred in the occipital area ($F(1,35) = 4.27$, $p < 0.05$). For the AD group, the largest differences for task relevancy occurred in the central area ($F(1,35) = 8.70$, $p < 0.01$).

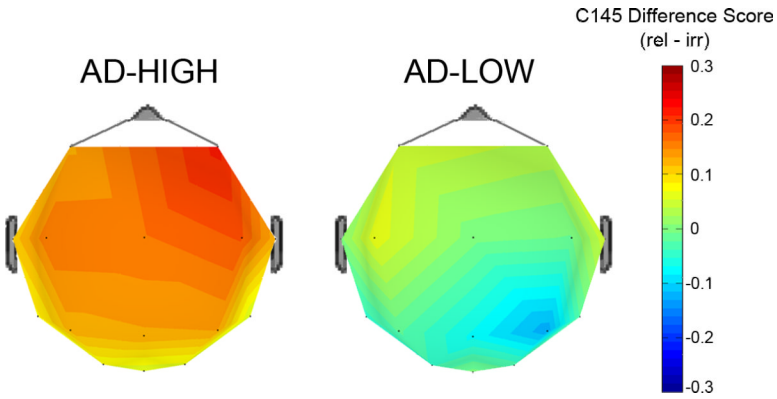

Figure 3.

Topographical patterns for C145 task relevancy difference scores for the AD-high and AD-low subgroups. C145 difference scores (rel – irr) measure the relevancy effect with other effects removed (e.g., individual differences, physical stimulus differences, stimulus category differences). The spatial distribution (based on the International 10-20 System) of difference scores indicates where the differences between C145 amplitudes for processing relevant and irrelevant stimuli were larger for each group. The AD-high group generally showed much more differential processing of task relevancy than the AD-low group at this short-latency ERP component, particularly in the central region (electrodes C3, CZ, C4). Although the AD-high group also appeared to show a large relevancy difference at right, frontal electrode F4, this effect was not significant. This position tends to have large amplitude variations due to eye movements.

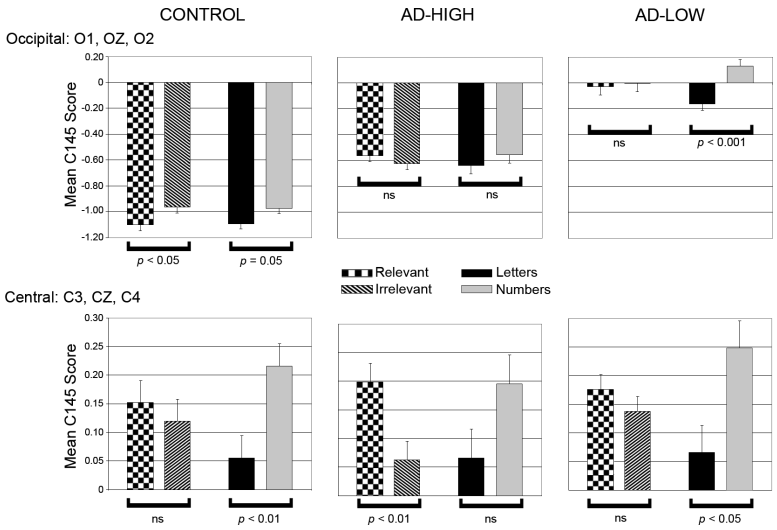

Figure 4.

C145 component scores as affected by Number-Letter task conditions (task relevancy, stimulus type) for Control, AD high performance, and AD low performance groups in occipital and central regions. Error bars reflect SEM (effect × subjects error term used in ANOVA). ns = not significant ($p > 0.05$). For the Control group at the occipital region, there was a significant task relevancy effect ($F(1,35) = 4.27$) and a stimulus type effect ($F(1,35) = 5.92$). For the Control group at the central region, there was a significant stimulus type effect ($F(1,35) = 11.89$) but not a significant task relevancy effect. For the AD-high group at the occipital region, there were no significant effects. At the central region, the AD-high group had a significant task relevancy effect ($F(1,18) = 8.97$) and a nearly significant stimulus type effect ($F(1,18) = 3.31$, $p = 0.09$). The AD-low group had only significant stimulus type effects at the occipital ($F(1,16) = 16.48$) and central region ($F(1,16) = 7.29$).

Table 1

Demographical, neuropsychological, and behavioral results for Control and AD groups.

Group	Age	Education	MMSE*	% Correct†
Control *(n=36)*	74.2 (7.1)	15.5 (2.4)	29.1 (0.9)	98.3 (1.7)
AD *(n=36)*	74.6 (7.2)	14.4 (2.8)	24.5 (2.6)	86.7 (11.3)
AD Subgroups				
AD-High *(n = 19)*	74.7 (6.0)	14.8 (3.0)	24.9 (2.4)	95.0 (2.8)
AD-Low *(n=17)*	74.4 (8.6)	13.9 (2.7)	24.1 (2.9)	77.4 (9.8)

Note. Values appear as mean (SD). The age and education information is in number of years. Both the AD and Control groups contained 18 women and 18 men, totaling 36 subjects in each group. There was no significant group effect, gender effect, or group by gender interaction for the age and education demographics between the AD and Control groups. The AD group was divided into AD Subgroups by performance accuracy on the Number-Letter task (>90% accuracy was considered high performance). The AD-high subgroup contained nine women and ten men. The AD-low subgroup contained nine women and eight men. In these subgroups, subjects were matched demographically for age, education, and severity of dementia (as measured by the MMSE). There was no significant subgroup effect, gender effect, or subgroup by gender interaction for age and education. There was no significant AD subgroup effect on MMSE score but there was a significant gender effect ($F(1,35) = 5.59$, $p < 0.05$).

*MMSE = Mini-Mental State Examination [28]. These MMSE scores were collected independently of those used in clinical diagnosis.

†Number of correctly answered trials divided by the total number of trials for the Number-Letter paradigm. Only correct trials were used in subsequent ERP analyses.

Table 2

Correlations between Number-Letter task accuracy and C145 task relevancy component scores at occipital and central locations.

	Occipital		Central	
	r	***p***	***r***	***p***
Subjects Included: Control, AD-high, AD-low (n = 72)				
Rel	-0.42	0.0002	-0.12	0.31
Irr	-0.43	0.0002	-0.17	0.16
Rel-Irr	-0.04	0.74	0.09	0.47
Subjects Included: AD-high, AD-low (n=36)				
Rel	-0.29	0.09	-0.13	0.45
Irr	-0.38	0.02	-0.28	0.09
Rel-Irr	0.20	0.23	0.34	0.04

Note. Correlations were performed using C145 component scores for relevancy task conditions at these brain locations. Rel = Relevant Stimuli. Irr = Irrelevant Stimuli. In addition to these results for Number-Letter task relevancy, task accuracy correlated significantly with stimulus types numbers (r = -0.41, n = 72, p = 0.0003) and letters (r = -0.44, n = 72, p = 0.0001) for all subjects.