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ERP C250 Shows the Elderly (Cognitively Normal, Alzheimer's Disease) Store More Stimuli in Short-Term Memory than Young Adults Do

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Abstract

Objective—To determine how aging and dementia affect the brain's initial storing of task-relevant and irrelevant information in short-term memory.

Methods—We used brain Event-Related Potentials (ERPs) to measure short-term memory storage (ERP component C250) in 36 Young Adults, 36 Normal Elderly, and 36 early-stage AD subjects. Participants performed the Number-Letter task, a cognitive paradigm requiring memory storage of a first relevant stimulus to compare it with a second stimulus.

Results—In Young Adults, C250 was more positive for the first task-relevant stimulus compared to all other stimuli. C250 in Normal Elderly and AD subjects was roughly the same to relevant and irrelevant stimuli in intratrial parts 1–3 but not 4. The AD group had lower C250 to relevant stimuli in part 1.

Conclusions—Both normal aging and dementia cause less differentiation of relevant from irrelevant information in initial storage. There was a large aging effect involving differences in the pattern of C250 responses of the Young Adult versus the Normal Elderly/AD groups. Also, a potential dementia effect was obtained.

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Conflict of interest

There were no conflicts of interest regarding this research.

Significance—C250 is a candidate tool for measuring short-term memory performance on a biological level, as well as a potential marker for memory changes due to normal aging and dementia.

Keywords

Event-Related Potentials (ERP); Electrophysiology; Alzheimer's disease (AD); Short-term memory; Principal Components Analysis (PCA); Short-latency ERP component C250

1. Introduction

Memory problems are a common complaint among the elderly population. Difficulties with storing information in short-term memory could be a serious culprit in age-related memory problems, as a diminished ability to identify and retain important information at an early-stage of information processing will have a negative bearing on anything that needs to be done with that information later. In addition, deficits of memory are a hallmark of numerous diseases that commonly afflict the elderly, including amnestic Mild Cognitive Impairment (Petersen et al., 2013) and Alzheimer's disease (AD) (McKhann et al., 1984). It is not well understood how age impacts working memory operations and what causes normal aging processes to deviate into memory impairment. Biological markers that index specific memory processes would, therefore, be of tremendous use to both the general study of aging and the study of age-related cognitive deterioration (Dubois et al., 2014).

Event-Related Potentials (ERPs) measure voltage changes among populations of co-localized neurons in response to discrete stimuli. ERPs can therefore reflect functional aspects of neural networks (Picton et al., 2000). ERPs are particularly well-suited to studying memory operations. Unlike other neural imaging methods such as PET and fMRI (Wager et al., 2007), electroencephalography (EEG) and the ERPs derived from it boast high-temporal resolution (on the order of milliseconds) which allows catching the early, post-stimulus processing when the identification and storage of information important to completing a task likely occurs. When manipulated by a cognitive task with separable task conditions, ERPs and their underlying components can provide direct, quantitative brain indices of abstract cognitive processes. The behavior of ERP components under varied task conditions has been related to memory processes (Chapman, McCrary and Chapman, 1978; Friedman, Vaughan and Erlenmeyer-Kimling, 1978; Chapman, McCrary and Chapman, 1981; Ruchkin et al., 1990; Begleiter, Porjesz and Wang, 1993; Polich, 2007; Rugg and Curran, 2007; Fukuda, Awh and Vogel, 2010), recognition and familiarity (Pfütze, Sommer and Schweinberger, 2002; Trenner et al., 2004; Morgan et al., 2008), semantic meaning (Chapman et al., 1978), stimulus expectancy (Walter et al., 1964; Arbel et al., 2011), executive functioning (Begleiter and Porjesz, 1975), and stimulus relevance (Chapman and Bragdon, 1964; Chapman, 1965; Chapman et al., 2013a), among others. ERP components have also proven useful in measuring age-related versus dementia-related changes in cognition and memory (Chapman et al., 2007; Missonnier et al., 2007; Rossini et al., 2007; Jackson and Snyder, 2008; Olichney et al., 2008; Chapman et al., 2011; Cespón, Galdo-Álvarez and Díaz, 2013; Friedman, 2013). However, post-stimulus ERP components of relatively short-latency have not been as well studied in the context of aging and AD.

Defining and validating a reliable ERP measure of faltering memory processes would prove advantageous to the studies of memory, aging, and dementia and disease processes.

ERP component C250 (maximal at 250 ms post-stimulus) has been shown to index the storage of a stimulus in short-term memory (Chapman, McCrary and Chapman, 1978; 1981; Chapman et al., 2015). C250 is of particular interest since it precedes many other ERP measures that concern working memory maintenance and updating, including P300 (Polich, 2007), FN400 (Olichney et al., 2008; Olichney et al., 2011), and P600 or Late Positive Component (Olichney et al., 2008; Olichney et al., 2011). C250 concerns the immediate storage of a stimulus rather than maintenance or retrieval. In young adults, C250 amplitudes are increased over central and frontal areas in response to relevant task stimuli that require storage as opposed to those that are relevant but do not require storage and those that are not relevant. More so than other components studied, including P300 and its subcomponents of P3a and P3b, C250 amplitudes predict behavioral recall of a stimulus that was stored in short-term memory as reflected by the strong correlation of C250 with behavioral memory probe data (Chapman et al., 2015). This suggests C250 may be a useful measure in tracking age-related and disease-related changes in short-term memory. The process of translating information from fleeting sensory registers to more lasting short-term storage could be altered during the course of normal aging, perhaps manifesting in many of the memory difficulties of which elderly individuals often complain. In addition, there is evidence that individuals with early-stage dementia may have problems with identifying task-relevant information and storing it (Chapman et al., 2007; Chapman et al., 2013a). If information is not stored properly, this deficit would affect all subsequent processing that depends on using that information.

In this article, we examine C250 as an electrophysiological index of short-term memory storage during both aging and dementia. Here our emphasis is not on the capacity of working memory, although a great deal of research has been done on this topic (Vogel and Machizawa, 2004). Rather, we are investigating the functional aspects of the initial storage of information in short-term memory and how these functional properties change with age and cognitive impairment. We will compare C250 brain responses in Young Adults, Normal Elderly, and elderly diagnosed with early-stage AD. These responses were measured while the participants performed the Number-Letter task, which contains a random sequence of both two irrelevant stimuli which may be ignored and two relevant stimuli that are used in a comparison task. We use contrasts between Young Adults and Normal Elderly to study aging and comparisons between Normal Elderly and like-aged AD to study disease effects with aging held constant. These comparisons will help determine how the memory storage process changes and whether C250 can detect those changes.

2. Methods

2.1 Study Subjects

We studied 36 elderly individuals diagnosed with early-stage Alzheimer's disease (AD), 36 like-aged Normal Elderly, and 36 Young Adults (Table 1), totaling 108[1]. The AD and Normal Elderly subjects were recruited from the Memory Disorders Clinic at the University of Rochester and other affiliated University of Rochester clinics. All AD subjects were

evaluated by memory-disorder physicians and met established clinical criteria for AD (NINCDS-ADRDA) (McKhann et al., 1984) and DSM-4TR criteria for Dementia of the Alzheimer's Type (American Psychiatric Association, 2000) and were considered early in the course of the disease. This study began prior to the acceptance of new research diagnostic criteria for AD (Dubois et al., 2007; Dubois et al., 2014) 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 a comprehensive clinical assessment of dementia. Normal Elderly subjects were cognitively normal for their age and demographically similar to the AD participants. Most Normal Elderly participants were selected from the same Memory Disorders Clinic and underwent the same clinical assessment for cognitive impairment. Some Normal Elderly participants were volunteers from the community but were evaluated with a comprehensive neuropsychological test battery designed to assess memory impairment. Young Adults were student volunteers from the University of Rochester campus.

There were no significant group or gender differences for age and education between the AD and Normal Elderly groups at baseline (Table 1). However, as expected the early-stage AD group had a significantly lower mean score ($F(1, 70) = 90.41$, $p < 0.0001$) on the Mini-Mental State Examination (MMSE) than the Normal Elderly group (Folstein, Folstein and McHugh, 1975). Between the Young Adults (mean age 21.8) and the Normal Elderly (mean age of 74.2), there were no differences in years of education, MMSE, or accuracy on our Number-Letter paradigm. 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 Normal Elderly 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 like this are possible even if the subject met strict research criteria as normal.

Exclusion criteria for both elderly 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 elderly 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.

2.2 The Number-Letter Paradigm

Our Number-Letter task (Chapman, 1965; Chapman et al., 1979; Chapman et al., 2007) manipulates working memory, stimulus relevancies and expectancies, and executive functions. The variety of different task and stimulus conditions provides the opportunity to measure ERPs such that the corresponding underlying ERP components can be empirically

[1]We used the G*Power software (Faul et al., 2009) to estimate sample size a priori. The program indicated that samples of 22 participants per group would provide power of 0.95 for the critical contrast of Relevancy for each Intratrial Part (alpha = 0.05, average correlation among repeated measures = 0.5, $\eta p^2 = 0.06$).

manipulated and differentiated. Previous research with this task has shown it to manipulate many common and useful cognitive ERP components.

During the Number-Letter paradigm, the subject's overall task was to compare two numbers for numeric order or to compare two letters for alphabetic order. Each trial consisted of a sequence of four stimuli briefly flashed in random order with fixed 750 ms intervals. The stimulus sequence contained two single-digit numbers (randomly selected from 1 to 6) and two letters (randomly selected from A to F). In addition, a white square (Blank) with a small black fixation initiated (750 ms before the first stimulus) and terminated (750 ms after the last stimulus) each trial and was not visible during the four-stimulus sequence. The subject then had up to three seconds to give his or her response. There was an intertrial interval of one second. All visual stimuli (blanks, letters, numbers) were large (height of 5.3° visual angle), white (55 cd/m^2), and presented briefly (~20 ms) on a dark background in the same central location on a computer monitor in a darkened room. 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 a letter-relevant block of trials, the participant compared the two letters in each trial for alphabetic order, and the numbers were irrelevant to the task. The same sequence of numbers and letters was used in both blocks of trials so that differences between relevant and irrelevant stimuli were not due to their visual properties or their order, which were identical. This control feature of the design was not explained to the subject, and the sequence of 408 stimuli (four stimuli per trial) in a block of 102 trials was not likely to be remembered. Subjects were given practice trials before the first experimental block to ensure they understood the task.

At the end of each trial, the participant said "Forward", "Backward", or "Same" to indicate the numeric or alphabetic order of the two relevant stimuli. The numbers and letters were randomly chosen with replacement, and the sequences of numbers and letters in the four temporal intratrial parts were randomized (constraint of two numbers and two letters per trial). This randomization was unique for each subject. Either the number-relevant block of 102 trials or the letter-relevant block of 102 trials was presented first, followed by the other relevant stimulus block. This totaled 204 trials. Importantly, memory storage of the first relevant stimulus, which randomly appeared in intratrial part 1 or 2, was required in order to compare it with the second relevant stimulus, which randomly appeared in part 3 or 4.

Although repeating a stimulus within a trial could elicit a repetition effect on ERPs and performance, this effect should be small (as these trials with identical stimuli occurred 1/6 as often as trials of other types). Moreover, a repetition effect could only occur after the storage of the first relevant stimulus, which is what is emphasized in this paper.

The Number-Letter task permits examination of ERPs in response to 16 varying task conditions: two Task Relevancies (relevant, irrelevant), two Stimulus Types (letters, numbers), and four intratrial stimulus times (called Intratrial Parts). In most trials, the first relevant stimulus occurred in intratrial parts 1 or 2. The second occurred in parts 3 or 4[2].

2.3 Subject Performance on the Number-Letter Task

All subjects were capable of performing the Number-Letter task (Table 1). The percent of trials correctly answered was 87% for the AD group, 98% for the Normal Elderly group, and 98% for the Young Adult group. Both the Young Adult and Normal Elderly groups significantly outperformed the AD group ($F(1, 70) = 37.10$, $p < 0.0001$ and $F(1, 70) = 39.30$, $p < 0.0001$, respectively). The Young Adult group did not perform significantly better than the Normal Elderly group ($F(1, 70) = 0.71$, $p = 0.40$). No main gender effect or group by gender interaction occurred on Number-Letter task performance.

2.4 Short-Term Memory Probe

To determine empirically which stimuli were in fact being stored in short-term memory during the Number-Letter task, we also performed a behavioral probe on a separate set of 52 young, college-aged individuals. This also validated the assumptions of the task: that performance required a subject to store the first relevant stimulus in short-term memory in order to compare it with the second, and that storage of all other stimuli is optional.

While the primary task on each trial was to compare the two relevant stimuli, the memory probe test was occasionally inserted after the stimulus being probed. At this point, the experimenter asked the subject what was the last stimulus he/she had seen. Two blank flashes (delivered at 750 ms and 1500 ms after the stimulus) were shown after the subject saw the number or letter stimulus being probed. These blank flashes (Blanks) were used to mask the probed stimulus and to delay the recall report in order to reduce the effects of very short-term sensory (iconic) registers. The subject's verbal response (the particular letter or number) was recorded. This probing procedure was performed without warning and rarely (7.8% of trials). There was one probe for each of the eight conditions (Relevant or Irrelevant by Intratrial Parts 1–4) for each block (Number-Relevant or Letter-Relevant) of 102 trials, resulting in sixteen total probes after the two blocks of trials. Percentage of correct responses over the group were converted to probit scores (z-score units), e.g. 50% and 98% correct produce 0.00 and 2.05 probit scores, respectively. As noted above, the behavioral memory-recall data were obtained from a separate group of young subjects (Chapman, McCrary and Chapman, 1978).

2.5 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 left outer canthus (EOG) with reference to linked earlobes) were used to non-invasively record electrical brain activity while the participant performed the Number-Letter task. The EOG detected blinks and eye movements. Frequency bandpass of the Grass amplifiers was 0.1-100 Hz. Beginning 30 ms before each stimulus presentation, 155 digital samples were digitized at 5 ms intervals. Subsequently, the physiological data were digitally filtered to pass frequencies below 60 Hz, and artifact criteria were based on the CZ and EOG channels to exclude those 775 ms epochs whose post-stimulus voltage

[2]It was possible for the first relevant stimulus to occur in intratrial part 3 and, on other occasions, for the second relevant stimulus to occur in intratrial part 2. Each happened rarely and was done so that the subject would not necessarily make assumptions about when the relevant stimuli had to occur. For computational simplicity, these trials were discarded and therefore were not included in the PCA or any subsequent analysis.

range exceeded 200 μV or whose baseline exceeded ± 250 μV (baseline was mean of 30 ms pre-stimulus). We used wide ranges for EEG to allow a reasonable amount of brain activity to enter into the averaging that produces each ERP. If eye movements produced a large, systematic effect, the PCA should isolate them in the form of a component, which it did (see Section 2.6). When the exclusion criteria were met, the 775 ms epoch for that stimulus was discarded on all channels. The ERPs were based on correct trials and data not rejected for artifacts. Mean artifact rejection rate was 4.9% (SD = 9.9%). The number of samples in each ERP for each group are available in Supplementary Table S1.

The baselines for each channel were digitally reset at the beginning of each trial before the first fixation flash (Blank) without any further DC adjustments for the remaining stimuli in that trial so that we could detect and separate overlapping components that are starting early or persisting later than a single stimulus. As discussed in section 2.6, we were able to extract both Slow Wave and CNV in our analysis, which are long-lasting components that can persist across stimuli. This would have been hindered by resetting the baseline to each intratrial part. In addition, because PCA with an orthogonal rotation produces components that are uncorrelated with one another, any baseline drifting that could be due to long-lasting components will not affect other components.

2.6 Event-related Potential Components: Principal Components Analysis

We derived ERPs for each subject from his/her EEG vectors (155 time points per electrode for each stimulus) by averaging each vector separately for each of the 16 task conditions in this experimental design (plus the two Blanks – see above) and for each of the 16 electrodes. A topography of average ERP waveforms for each group for relevant task conditions appears in Supplementary Figure S1.

Kayser and Tenke (Kayser and Tenke, 2005) 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, Varimax Principal Components Analysis (PCA) (Chapman and McCrary, 1995; Dien, 1998; Picton et al., 2000; Kayser and Tenke, 2005), to identify and develop operational measures of the ERP component construct. Volume conduction in the brain suggests an additive ERP model, which underlies the PCA process in extracting the component structure (Chapman and McCrary, 1995). PCA can be employed to separate functionally distinct events. It provides a parsimonious measurement system that relies on the implicit structure of the data in developing composite measures of brain activity without preselecting relevant time zones. It also derives a solution that respects the possibility of components that overlap in time. This is of particular concern when measuring C250, which often appears as a shoulder to an earlier exogenous sensory component. PCA forms weighted linear combinations of the original measurements that capture most of the relevant variance and/or allows temporal or spatial overlap of components that are orthogonal. Our approach to PCA used ERP time points as the variables, with subjects, electrode sites, and task conditions as cases. This allowed the computation of component scores (amplitudes of the components) for each of these cases.

We submitted to a PCA the ERP data from the three groups of 36 subjects each (described in Section 2.1) along with an additional 36 subjects diagnosed with Mild Cognitive Impairment (MCI) (see the Supplementary Material for the MCI demographic information). This set of 144 varied subjects was used to solve for ERP components that would be more generalizable to a wider array of individuals (Carroll, 1993) with varying cognitive and memory capabilities. 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 (Fabrigar et al., 1999). The data matrix that entered the PCA contained 155 variables (time points per epoch) and 41, 472 cases (144 subjects X 16 electrodes X ((2 Task Relevancy X 2 Stimulus Types X 4 Intratrial Parts) + 2 Blanks). This PCA was computed using a correlation matrix.[3]

From the PCA, we retained nine ERP components that accounted for 98% of the total variance. Previous work with this paradigm and our experience with the ERP components it extracts led us to retaining this set. The components extracted included well-known components that we have derived and studied before with the Number-Letter paradigm, such as P300 (Chapman and Bragdon, 1964; Chapman, 1965; Chapman, McCrary and Chapman, 1978; Polich, 2004; 2007), CNV (Walter et al., 1964), C145 (Chapman et al., 2013a), C250 (called the storage component in Chapman et al. (1978; 1981)), and other short- and long-latency components (for graphs of these components, see Supplementary Figure S2). One component represented an ocular-related artifact (with a maximum at 15 ms post-stimulus and no activity around 250 ms post-stimulus) (Yuval-Greenberg et al., 2008) so it is not discussed further. Extracting an EOG factor means that other ERP factors may be mathematically independent of it.

After Varimax rotation, ERP component C250 was the 4th highest ranked component with respect to the variance for which it accounted. C250 accounted for 1.4% of the variance explained by the set of nine components. Long-lasting components, such as Slow Wave or CNV, should account for more variance than briefer components, such as C250, given that other characteristics are equal.

Part of the PCA output (the component loadings) represents the temporal waveforms of each ERP component (Chapman et al., 2007) (Figure 1). Multiplying the vector of C250 component loadings by the vector of standard deviations for each time point and by the average component score for each condition for each group produces the component waveform with the metric restored. The SAS 9.1.3 and 9.3 procedure FACTOR was used to generate the component solution and calculate the ERP measures (Khattree and Naik, 2000).

We retained the C250 component scores for further analysis. There were 16 C250 ERP component scores, one for each Number-Letter task condition (two relevancy x two stimulus types x four intratrial parts) for each electrode site, totaling 256 scores for each subject. To simplify further analyses and reduce the impact of multiple statistical comparisons, we

[3]For a discussion comparing PCA performed on correlation versus covariance matrices, see Chapman and McCrary, 1995; Dien 2006; Kayser and Tenke, 2006. We determined empirically with the present dataset that PCAs based on the correlation or covariance matrices produced nearly identical ERP components (comparisons of the two methods by correlations between their output vectors for each component produced *r's* > 0.99).

averaged C250 component scores for the 16 electrode sites into the following regions of interest: frontal (F3, F4), central (C3, CZ, C4), parietal (P3, PZ, P4), and occipital (O2, OZ, O1). Topographical maps (Figure 2 – discussed in the next section) were generated using the Bioelectromagnetism Toolbox (Weber, 2009) in MATLAB R2013a (MathWorks, 2011). The topomaps showed no striking laterality differences.

2.7 Statistical Comparisons

We examined difference in patterns of C250 effects among the Young Adult, Normal Elderly, and AD groups with ANOVA in a mixed repeated measures design that featured 3 Groups (Young Adults, Normal Elderly, AD) X 2 Task Relevancy (Relevant, Irrelevant) X 2 Stimulus Types (Numbers, Letters) X 4 Intratrial Parts X 4 Scalp Regions (Frontal, Central, Parietal, Occipital). When necessary, p values were corrected using the Huynh-Feldt-Lecoutre Epsilon. We performed all statistical procedures in SAS (SAS Institute Inc., 2014) using PROC GLM for ANOVA and PROC CORR for correlation analyses. In the following sections effect sizes were calculated as partial η^2 (η_p^2) and p values were considered statistically significant at $p = 0.05$. Comparisons among three groups do not require adjustments of alpha for multiple tests (Myers, Well and Lorch, 2010).

3. Results

3.1 Visual Description of Findings

Mean C250 responses from each electrode were averaged over all experimental conditions for each group to make the topographical maps in Figure 2. C250 amplitudes generally increased in positivity from anterior to posterior scalp locations. This is particularly true for the Normal Elderly and AD groups, which had more positive C250 responses over the occipital region than they did over the frontal region. Second, C250 does in fact have measurable, differentiable amplitudes in elderly individuals (Figure 2) that are at least as positive, or more so, than in young subjects. The pattern of experimental task effects must be examined in order to detect more important differences in C250 processing among the groups.

Previous work (Chapman et al., 2015) indicated that a relatively positive-going pattern of C250 responses in Young Adults signified short-term memory storage. We visually examined C250 for each intratrial part (difference score of relevant stimuli – irrelevant stimuli) (Figure 3) to see how aging and dementia might affect the spatial distribution of brain responses during memory storage. During intratrial parts 1 and 2, Young Adults show a much larger, more positive response to relevant stimuli than to irrelevant stimuli at most of the electrode sites but particularly at central and frontal locations. During parts 3 and 4, they tend to have little difference between relevant and irrelevant stimuli or more positive responses to irrelevant stimuli. A very different pattern of effects was seen in the Normal Elderly group, which showed diminished differentiation of relevant from irrelevant stimuli across all parts with exception of the final part (part 4). At part 4, they demonstrated a more positive response to relevant rather than irrelevant stimuli. This effect was repeated in the AD group, though the AD group had an even less positive response to relevant stimuli in intratrial part 1 than the Normal Elderly did. Still, the pattern of C250 responses in the two

elderly groups (Normal and AD) seemed much more similar to each other's than to that of the Young Adults.

3.2 Number-Letter Task Effects

Short-term memory storage is a function of both stimulus relevance and the temporal position (intratrial parts) of the stimulus in the sequence of numbers and letters (as depicted in Figure 3). Given that, we examined Number-Letter task effects (Task Relevancy, Stimulus Type, and Intratrial Part) and how they interacted with scalp regions for each subject group (Figure 4) to determine how these varying conditions affected memory storage and how memory storage was, in turn, affected by aging and dementia. We found significant main effects as well as interactions in our mixed design ANOVA. Two four-way interactions were significant.

We found a significant Relevancy X Region X Stimulus X Group interaction ($F(6, 315) = 3.32$, $p = 0.01$, $\eta_p^{2=} 0.04$, $\varepsilon = 0.61$). While Stimulus Type in conjunction with relevance, region, and groups did influence C250 processing (see the Supplementary Material), the relationship between Stimulus Type and C250 was of less interest here. We believe these Stimulus Type effects (numbers vs. letters) may be due to the alphabetic comparison task being generally more difficult and less automatic than its numeric counterpart. Because our experiment presents the same physical stimuli as relevant and irrelevant in different blocks of trials, we can separate the cognitive effects of interest here from stimulus effects. Furthermore, Stimulus Type did not interact with Intratrial Part, which is a key aspect of memory storage in this design.

There was also a significant Relevancy X Region X Part X Group interaction ($F(18, 945) = 3.99$, $p = 0.0006$, $\eta_p^2 = 0.14$, $\varepsilon = 0.35$), which was more important as this relationship among Relevancy, Part, and Group is key in terms of how aging and dementia impact short-term memory storage. Each group showed a significant Region X Relevancy X Part interaction: Young Adults: $F(9, 315) = 5.09$, $p = 0.0004$, $\eta_p^2 = 0.13$, $\varepsilon = 0.50$; Normal Elderly: $F(9, 315) = 3.05$, $p = 0.05$, $\eta_p^2 = 0.08$, $\varepsilon = 0.20$; AD: $F(9, 315) = 3.18$, $p = 0.01$, $\eta_p^2 = 0.08$, $\varepsilon = 0.51$. Given this, we separately examined the Relevancy X Part interaction at each region for each group.

3.2.1 Task Effects for the Young Adult Group—An ANOVA for the Young Adult group used a Relevancy X Part model at each region (Supplementary Table S2). At the frontal region, the Relevancy X Part interaction was significant ($F(3, 105) = 11.08$, $p < 0.0001$, $\eta_p^2 = 0.24$, $\varepsilon = 0.88$), so we examined Relevancy effects for each intratrial part (Table 2) to determine how trial sequence influences processing of task relevancy. In intratrial parts 1 and 2, relevant stimuli elicited a more positive C250 amplitude than irrelevant stimuli (the largest effect size occurred in part 1, where $\eta_p^2 = 0.24$). Conversely, in part 4 there was a large effect ($\eta_p^2 = 0.23$) involving C250 amplitudes for relevant stimuli being significantly *less* positive than those for irrelevant stimuli. There was no significant relevancy difference in part 3. These effects can be seen in Figures 3 and 4. Our results here fit our model of short-term memory storage (Chapman et al., 2015).

There was also a Relevancy X Part interaction for the Young Adults at the central region ($F(3, 105) = 6.38$, $p = 0.0005$, $\eta_p^2 = 0.15$, $\varepsilon = 1.05$). Again, this was followed by separate analysis of relevancy for each part. Generally, effects in the central region were similar to those seen at the frontal region, where Young Adults again showed significantly more positive C250 responses to relevant stimuli in intratrial parts 1 and 2 and significantly less positive C250 responses to relevant stimuli in part 4 (Table 2).

This pattern of effects for the Young Adult group changed slightly at more posterior electrode sites. At the parietal region and occipital regions, again there were significant Relevancy X Part interactions (parietal: $F(3, 105) = 5.44$, $p = 0.002$, $\eta_p^2 = 0.13$, $\varepsilon = 1.05$; occipital: $F(3, 105) = 4.76$, $p = 0.004$, $\eta_p^2 = 0.12$, $\varepsilon = 1.07$). Young Adults showed a significant Relevancy effect for intratrial part 4 such that C250 was less positive for relevant than for irrelevant stimuli at both regions (Table 2). This effect was seen again for part 3 at the occipital region ($\eta_p^2 = 0.10$). Additionally, at the parietal region, C250 for relevant stimuli in part 1 was significantly more positive than C250 for irrelevant stimuli ($\eta_p^2 = 0.11$). In summary, the significant storage effects seen for relevant stimuli in the first two intratrial parts at frontal and central regions were weaker in the parietal region and absent in the occipital region.

3.2.2 Task Effects for the Normal Elderly Group—The Normal Elderly showed fewer significant Relevancy X Part interactions across the regions studied than the Young Adults did (Supplementary Table S2). Because the Relevancy X Part interaction fell short of significance at the frontal region ($F(3, 105) = 2.96$, $p = 0.08$, $\varepsilon = 0.44$), any relevant/irrelevant comparisons for individual intratrial parts need to be treated with caution. However, in view of findings for central region described below, it is interesting that the frontal results exhibited a pattern such that for part 4 relevant stimuli had more positive C250 amplitudes than irrelevant stimuli ($\eta_p^2 = 0.10$; Table 2). The Normal Elderly produced a Relevancy X Part interaction at the central region ($F(3, 105) = 4.99$, $p = 0.007$, $\eta_p^2 = 0.12$, $\varepsilon = 0.74$). Individual comparisons (Table 2) indicated that there was a significant Relevancy effect only for part 4 ($\eta_p^2 = 0.15$) where again relevant stimuli had more positive C250 amplitudes than irrelevant stimuli (Table 2). In contrast, the Relevancy X Part interactions were not significant at the parietal ($F(3, 105) = 1.67$, $p = 0.19$, $\varepsilon = 0.82$) or occipital ($F(3, 105) = 0.01$, $p = 1.00$, $\varepsilon = 0.80$) regions.

3.2.3 Task Effects for the Alzheimer's Disease Group—We also tested the Relevancy X Part model for the AD group separately for each scalp region (Supplementary Table S2). There was a significant Relevancy X Part interaction at the frontal region ($F(3, 105) = 5.80$, $p = 0.001$, $\eta_p^2 = 0.14$, $\varepsilon = 0.95$). Like the Normal Elderly group, the AD group showed significantly larger C250 responses to relevant than irrelevant stimuli in only part 4 ($\eta_p^2 = 0.21$) (Table 2). Similarly, the AD group also showed a Relevancy X Part interaction at the central region ($F(3, 105) = 7.06$, $p = 0.0005$, $\eta_p^2 = 0.17$, $\varepsilon = 0.88$). As was the case at the frontal region, C250 responses at part 4 were more positive to relevant stimuli than to irrelevant stimuli ($\eta_p^2 = 0.27$; Table 2). Again, the large differentiation between relevant and irrelevant stimuli in the last intratrial part can be seen in Figures 3 and 4. At the parietal regions, AD subjects also showed a significant Relevancy x Part interaction ($F(3, 105) =$

3.31, $p = 0.03$, $\eta_p^2 = 0.09$, $\varepsilon = 0.84$). However, the differences between relevant and irrelevant stimuli were not significant for any parts. The only apparent exception occurred at part 4, where C250 for relevant stimuli tended to be more positive than for irrelevant stimuli ($\eta_p^2 = 0.10$; Table 2). Finally, there was no significant Relevancy X Part interaction at the occipital region ($F(3, 105) = 1.34$, $p = 0.27$, $\varepsilon = 0.83$).

3.3 C250 as an Index of Memory Storage Confirmed by a Behavioral Probe

C250 amplitudes represent short-term memory storage of a stimulus in Young Adults; previous work with a memory probe test conducted during the Number-Letter paradigm on another group of young adults (Chapman, McCrary and Chapman, 1978) showed C250 component scores were highly correlated with mean recall of the stimuli in the 16 experimental conditions (for example, relevant numbers in intratrial part 2) (Chapman et al., 2015). Here we tested correlations between these mean behavioral recall scores for each of the 16 conditions from the previously described independent young group and mean C250 component scores at central electrodes for each of our three subject groups. Previous work with C250 in young individuals indicated its maximal effects occurred over central brain regions (Chapman et al., 2015). This finding agreed with the current data (Figures 2 and 3).

As shown in Figure 5, which contains a scatter plot of C250 responses for each group and behavioral probe data, the correlation was high ($r = 0.63$) for this group of Young Adults. Inspection of the means shows that those stimuli whose storage was required by the task (relevant numbers and letters in intratrial positions 1 and 2) had the largest C250 scores. The correlation was noticeably reduced for the Normal Elderly group ($r = 0.30$) and even more attenuated for the AD group ($r = -0.10$).

3.4 Comparisons between Groups

Given the different pattern of C250 amplitudes in the elderly groups, it could be suggested that they are simply not storing any stimuli at all in the context of this ERP component. In order to examine this hypothesis, we compared C250 responses to key storage conditions at central scalp regions between the Normal Elderly and the Young Adults. The overall pattern of C250 means for Task Relevancy and Intratrial Part (Figure 4) for the Normal Elderly was significantly different from the one observed for Young Adults (Relevancy X Intratrial Part X Group: $F(3, 210) = 6.46$, $p = 0.001$, $\eta_p^2 = 0.08$, $\varepsilon = 0.79$). However, the ways in which those differences occurred is essential in understanding memory storage in the elderly. Because the first relevant stimulus must be stored in order to perform the Number-Letter task, we decided to compare C250 responses to the first relevant stimulus between the Young Adult and Normal Elderly groups to determine whether the elderly are producing comparable C250 amplitudes to necessary relevant stimuli. The Normal Elderly produced relatively the same size C250 responses to relevant stimuli in parts 1 and 2 as the Young Adults did (mean of parts 1 and 2, $F(1, 70) = 0.93$, $p = 0.34$, $\eta_p^2 = 0.01$); this result would imply the Normal Elderly are storing these stimuli. In parts 3 and 4, however, the Normal Elderly showed more positive C250 responses to relevant stimuli than the Young Adults did (mean of parts 3 and 4, $F(1, 70) = 5.09$, $p = 0.03$, $\eta_p^2 = 0.07$). In fact, the Normal Elderly exhibited approximately the same size C250 to relevant stimuli across all parts ($F(3, 105) = 0.77$, $p = 0.51$, $\eta_p^2 = 0.02$), whereas the Young Adults had C250 responses to relevant stimuli

that were greatly influenced by part ($F(3, 105) = 17.37$, $p < 0.0001$, $\eta_p^2 = 0.34$). This set of results suggests the Normal Elderly may in fact be storing all relevant stimuli in contrast to the Young Adults' preferential storing of early relevant stimuli. This finding can be seen in Figures 3 and 4. While factors such as scalp thickness, size, and impedance can impact associated discrepancies in groups' ERP amplitudes, these factors would influence all parts in the trial sequence so they could not explain the differences discussed here.

We also compared the two elderly groups at the central region and found the Group X Relevancy X Part interaction to be not significant ($F(3, 210) = 0.14$, $p = 0.93$). This suggested that the AD group had a pattern of effects nearly the same as the Normal Elderly group.

However, visual inspection of the two elderly groups (Figure 4) suggested differences in the processing of the first relevant stimulus when it occurred in part 1. The AD group had less positive C250 responses for this condition than the Normal Elderly group had. We performed some post-hoc analyses to investigate this result. This general trend of less positive C250 responses for relevant stimuli in part 1 in the AD group than in the Normal Elderly group occurred for all regions (Table 2) and was nearly significant (overall Group effect for first relevant stimulus in part 1 averaged over all regions: $F(1, 70) = 3.36$, $p = 0.07$, $\eta_p^2 = 0.05$). This trend reached significance at the parietal region ($t(70) = -1.99$, $p = 0.05$). It should also be noted that the AD group did have a main effect of Part ($\eta_p^2 = 0.12$) at this region while the Normal Elderly group did not ($\eta_p^2 = 0.05$; Supplementary Table S2). At the parietal region, AD subjects demonstrated a C250 component score of −0.25 to relevant stimuli in part 1 as compared to parts 2, 3, and 4, which had scores of +0.03, +0.18, and +0.14, respectively. Conversely, the Normal Elderly exhibited component scores of +0.12 to relevant stimuli in part 1 as compared to parts 2, 3, and 4, which were +0.17, +0.14, and +0.14, respectively.

4. Discussion

The Number-Letter task provides particular advantages for the study of storing stimulus information in short-term memory. Assigning a number comparison task on a block of trials makes number stimuli be task relevant and letter stimuli be task irrelevant. On a different block of trials, assigning a letter comparison task makes the same number stimuli be task irrelevant and the same letter stimuli be task relevant. This arrangement allows comparison of information processing differences in ERPs evoked from these stimuli to be assessed while stimulus and order effects are controlled.

The interaction between Task Relevancy and Intratrial Part offers two key conditions: (1) stimuli for which memory storage is required to complete the task and (2) stimuli for which storage is optional. Storage of the first relevant stimulus, which randomly appears in intratrial part 1 or 2, is required in order to later perform the comparison with the second relevant stimulus, which randomly occurs in intratrial part 3 or 4. Irrelevant stimuli in parts 1 and 2 and all stimuli in parts 3 and 4 do not require memory storage. The relevant stimulus appearing in part 3 or 4 is used by the subject to perform the comparison with the short-term memory of the first relevant stimulus in order to assess the numeric (or alphabetic) order of

the two relevant stimuli in that trial. Additionally, memory storage of irrelevant stimuli in any of the four intratrial parts is never required to complete the task successfully.

4.1 Memory Storage Effects in Young Adults

Clearly, Young Adults demonstrated a significantly more positive C250 to relevant, rather than to irrelevant, stimuli under some conditions (Figures 3 and 4). Specifically, Young Adults showed more positive C250 to relevant stimuli during the first half of the trial (parts 1 and 2) than during the second half (Table 2). This suggests that they successfully identified not only which stimuli were relevant but also the first relevant one in that trial for which memory storage was required. This pattern of effects occurred across the scalp, though it was the most pronounced at anterior electrodes.

Especially important in supporting a short-term memory interpretation of C250 is the correlation between C250 amplitudes and the behavioral probe data ($r = 0.63$) for the Young Adults. The correlations of C250 amplitude with probe recall accuracy confirms that both relevant letters and relevant numbers in intratrial parts 1 and 2 were stored in short-term memory with greater success than under intratrial parts 3 and 4. These results show that Young Adults are in fact remembering the stimuli according to the task parameters, and this finding is associated with a more positive C250 response for relevant stimuli in parts 1 and 2 (Figures 4 and 5).

This is the fourth instance with different samples of young individuals for whom we have observed this pattern of C250 results (Chapman, McCrary and Chapman, 1978; 1981; Chapman et al., 2015). Also, other researchers using different paradigms have found similar positive activity with a comparable component (Begleiter, Porjesz and Wang, 1993) concerning working memory storage occurring over prefrontal and anterior areas in young adults (Ko et al., 2014). The sturdiness of this relationship leads us to utilize C250 as an index of storage in short-term memory that can be applied to other subject groups to study how short-term storage might vary with aging and cognitive conditions.

4.2 Memory Storage and Aging

The present results clearly indicate that aging alters the conditions under which the brain performs short-term memory storage. The distinct differentiation of task-relevant stimuli from irrelevant stimuli found in Young Adults was noticeably absent in the Normal Elderly group during the first three parts of the trial (Figures 3, 4, and Table 2). Additionally, the results of Normal Elderly subjects had almost no correlation between their pattern of C250 responses to task stimuli and the memory probe data from a young adult group (Figure 5).

Before confirming the belief that aging dampens the brain’s ability to identify and retain information in short-term memory, some points should be considered. First, Normal Elderly were capable of performing the Number-Letter task well (98% correct). This accuracy level is not significantly lower than the performance of Young Adults. Second, although the pattern of C250 results in the Normal Elderly is not similar overall to the results of the Young Adult group, it is not because the elderly are failing in general to produce the same C250 amplitudes (Figures 2 and 4). Rather, the Normal Elderly are showing C250 amplitudes to the first relevant stimulus that are not different from those of the Young

Adults. In addition, at anterior regions the Normal Elderly demonstrate significantly more positive C250 amplitudes to the second relevant stimulus than the Young Adults. This pattern of results suggests that the Normal Elderly may be storing the second as well as the first relevant stimulus, whereas the Young Adult seem to limit their storage to the first relevant stimulus. Also, while Normal Elderly do not produce differentiable C250 responses to relevant and irrelevant stimuli in the first parts of the trial, Figure 3 and statistical results show that the Normal Elderly are in fact differentiating between relevant and irrelevant stimuli in intratrial part 4. Specifically, when the second irrelevant stimulus occurs in the last intratrial part, the Normal Elderly C250 positivity decreases sharply in comparison to both relevant and irrelevant stimuli in all other parts, particularly at anterior scalp areas (Figure 4). It is already possible to do the comparison task when the second irrelevant stimulus appears in this final part. This suggests the aging brain recognizes that the final irrelevant stimulus does not need to be stored.

A body of evidence supports the concept that elderly individuals have difficulty identifying or filtering out task-irrelevant information. Gazzaley et al. (2008) showed that older adults exhibited a selective deficit in suppressing task-irrelevant information during visual working memory encoding, but only in the early post-stimulus stages of visual processing. They attribute this effect to excessive attention to distracting information, which they supported with EEG spectral analysis of signals from frontal regions. Ko et al. (2014) suggested that visual working memory capacity is reduced by aging, but the complexities of the entire memory storage, maintenance, and retrieval processes must be studied to unravel how this occurs. Also, Jost et al. (2011) studied the contralateral delay activity of the EEG and determined that early in the retention interval older adults showed smaller filtering scores, which was indicative of retaining task-irrelevant information. This could correspond to what is seen in the present study regarding aged individuals at 250 ms post-stimulus.

What we have found concerning the aging brain storing more than the young brain is a rather unexpected result. As suggested above, it seems possible that this effect could stem from a “deficit” in differentiating relevant from irrelevant stimuli. However, arguing against this conclusion would be the result that Normal Elderly perform the Number-Letter task with the same high accuracy that the Young Adults do. Also, the C250 components of the Normal Elderly do clearly identify irrelevant stimuli in part 4 and treat them very differently than relevant stimuli in the same part. While the Young Adults appear to recognize that the first relevant stimulus is “necessary” to store in order to complete the task and that the second is not, elderly individuals do not seem to make this distinction. This alternate method of completing the task, such that both relevant stimuli are stored, could signify some sort of cognitive compensation. If pathways that quickly differentiate between relevant and irrelevant information have begun to break down, storing more stimuli could be a strategy for achieving a satisfactory behavioral result. Once the capacity of working memory is reached, however, such a method could prove disadvantageous because of limited resources. Much more research is needed to test this theory, including validating whether the elderly group is, in fact, storing more stimuli than just the first relevant one as the young do. In the present study, we did not administer the memory probe to the elderly participants for two reasons: first, we were concerned about the effects of task interference given a dual task situation, despite how rarely the probe occurs, and, secondly and more importantly, we were

concerned the probe might prove too difficult for cognitively impaired individuals. Gathering behavioral probe data from Normal Elderly subjects would be an important first step in further investigating how they perform short-term storage in contrast to how Young Adults do it.

4.3 Memory Storage and Dementia

The prominent aging effects obtained for the Normal Elderly were confirmed by the similar results for the AD group. As found for the Normal Elderly group, Relevancy effects for the AD group indicate they are not differentiating between relevant and irrelevant stimuli for most of the trial parts, save the last one where irrelevant stimuli showed a significantly less positive C250 response than relevant stimuli did. Also similar to the Normal Elderly group, the AD pattern of C250 effects did not correlate with the behavioral probe data from young individuals. In addition, visual inspection of the topomaps (Figures 2 and 3) and the pattern of C250 means for task conditions (Figure 4) confirm that the Normal Elderly and AD groups are very similar to each other. This similarity between the elderly groups was also supported by statistical analyses.

In previous work, in conjunction with other ERP measures, both relevant and irrelevant C250 responses contributed to the accurate diagnosis (Chapman et al., 2007) and prediction (Chapman et al., 2011) of AD in individuals. However, what we see in the current paradigm suggests that on its own, rather than in combination with other ERP markers, C250 shows similar results in both healthy aging and AD. Nevertheless, a small difference in the patterns of C250 responses suggests there may be subtle changes that could be telling (Figure 4). In intratrial part 1, the AD group generally had a less positive response to relevant stimuli than the Normal Elderly did. In fact, the AD group showed their least positive C250 scores toward relevant stimuli in part 1 (Table 2). This might suggest AD individuals are getting a “slow start” at processing the task on most trials. On the other hand, even though they performed the task significantly worse than the Normal Elderly did, the AD participants were still capable of correctly answering 87% of the trials on average. The question remains as to how they accomplish this. Perhaps they are differentially processing task-relevant information after storage, a possibility which could be measured through another ERP component besides C250.

4.4 Potential Limitations

Potential limitations of this study include: referral biases, medication and drug effects, and other medical issues that were not documented. Fortunately, there is some evidence that anticholinergic medications commonly used to treat early-stage AD have little influence on ERPs (Chapman et al., 2013b).

4.5 Uses of C250: Biomarker of Storage in Short-term Memory

C250 has now been shown and validated (Chapman, McCrary and Chapman, 1978; 1981; Chapman et al., 2015) to be a measure of short-term memory storage in Young Adults. Here we have applied it to study aging and dementia, but it could be used in both clinical and research settings to examine differences in memory storage for any number of conditions or purposes. It is not necessary for subsequent research or clinical application to compute the

PCA solution again once it has been derived. The ERP component loadings can be used to mathematically generate component scores for new individuals whose electrical brain activity was recorded while completing the Number-Letter task (Chapman et al., 2013b). These component scores can then be used to examine group differences (as was done here) or to diagnose or predict disease outcomes in individuals (Chapman et al., 2007; Chapman et al., 2011). Developing a common metric using a generalized set of subjects and applying this metric to new subjects has practical utility in that the same model of ERP components can be used to study different effects of interest.

The results in this article reveal some interesting information about short-term memory storage and how aging and dementia impact it. First, while the Normal Elderly and AD groups show comparably sized C250 responses to the Young Adult group (and more positive, particularly over posterior scalp locations), these responses and the patterns in which they occur do not completely correspond to short-term memory storage as seen in Young Adults. Second, aging and dementia may dampen the brain's ability to quickly isolate important stimuli for memory storage, which could lead the elderly into storing more stimuli than Young Adults do. As we postulate here, perhaps elderly subjects simply store everything they can until the last intratrial part, regardless of whether or not this information is relevant or necessary to completing the task. Further research is needed to explore these differences. In this study, we did not have behavioral probe data from our elderly subjects to directly confirm which stimuli can be recalled, and these data should be collected to validate our functional conclusions about C250 activity in the aging brain. These data would be key in determining if the Normal Elderly group are also storing the irrelevant stimuli with more likelihood than Young Adults do. Still, we believe we have shown that C250 is a sensitive marker for changes in short-term memory storage brought about by aging, and that can be a useful stepping stone to examine how other aspects of memory are altered as the brain gets older and sometimes diseased.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- In Young Adults, ERP C250 is more positive when stimuli that need to be later recalled are stored in short-term memory.
- Normal Elderly show similar C250 activation, as well as to other stimuli.
- Alzheimer's disease subjects are similar to Normal Elderly, except for a "slow start" trial-wise.

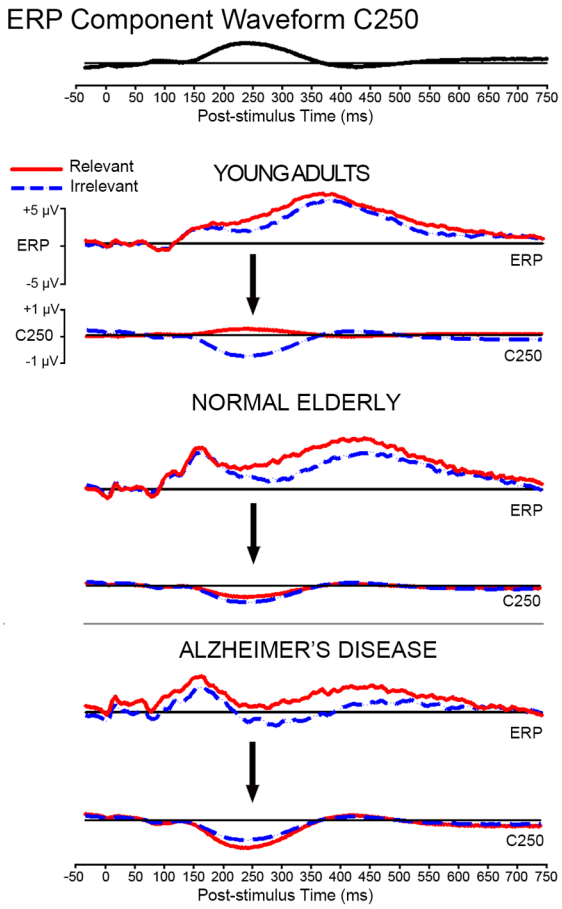

Figure 1.

Mean ERPs and ERP C250 component waveforms for each group at electrode F4 (chosen as an example). The model C250 waveform (top) was developed via PCA using a correlation matrix. Here the metric was restored by multiplying the vector of C250 component loadings by the vector of standard deviations for every time point. Below, C250 amplitudes are adjusted by multiplying the model waveform by the average component score for each group for the relevant and irrelevant task conditions. The Young Adult group showed a large C250 difference between relevant and irrelevant stimuli, while the Normal Elderly group showed essentially no difference and the AD had little difference. This figure illustrates the importance of using a formal method of measuring ERP components. For more information on using PCA to extract ERP components, see (Chapman and McCrary, 1995). For a grand mean ERP topography for each group, see Supplementary Figure S1.

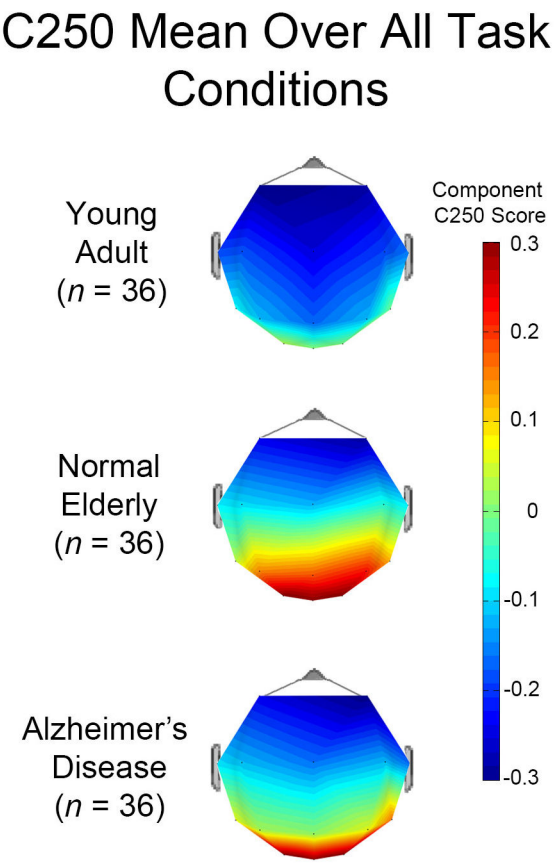

Figure 2.

Mean C250 component amplitudes over all Number-Letter task conditions for the Young Adult, Normal Elderly, and AD groups. C250 tended to increase from anterior to posterior brain areas (top to bottom in figure), particularly in the Normal Elderly and AD groups. There were no striking laterality (left versus right) differences. Note that by averaging across task conditions, the task effects that symbolize short-term storage are not visible in this figure (see Figures 3 and 4).

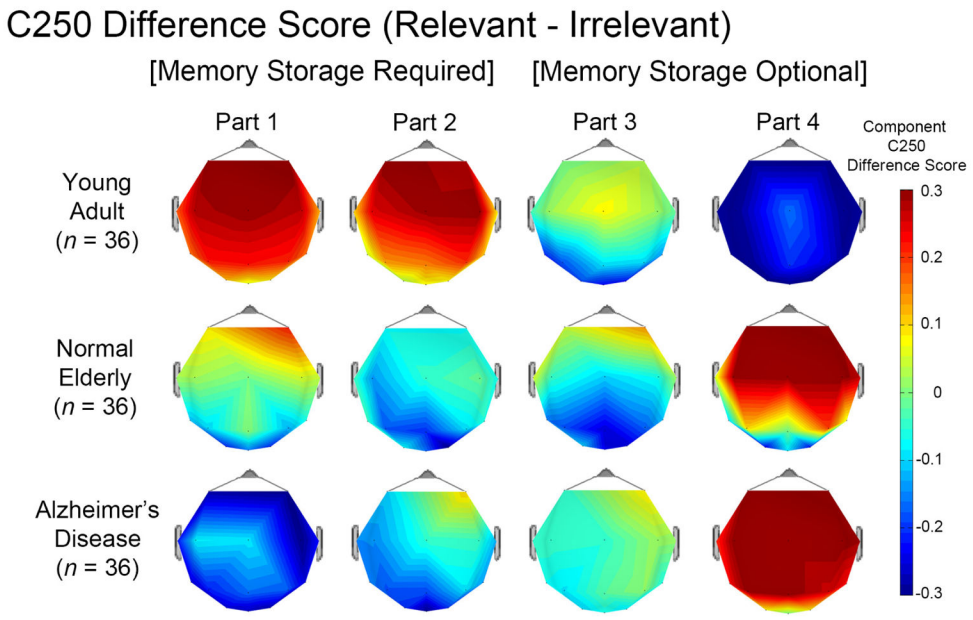

Figure 3.

Topographical maps of C250 responses for the difference between relevant and irrelevant stimuli (relevant – irrelevant) for the Young Adult, Normal Elderly, and AD groups. The Young Adult group had a large, positive response to relevant stimuli that required memory storage (parts 1 and 2). This C250 activity involved most of the scalp and disappeared for stimuli that did not require storage (parts 3 and 4). Conversely, the Normal Elderly and AD groups had a difference that was essentially zero (no difference between relevant and irrelevant stimuli) across most of the scalp for the stimuli that required storage. For both elderly groups, only part 4 showed a positive C250 activation (where relevant stimuli evoked a more positive C250 response).

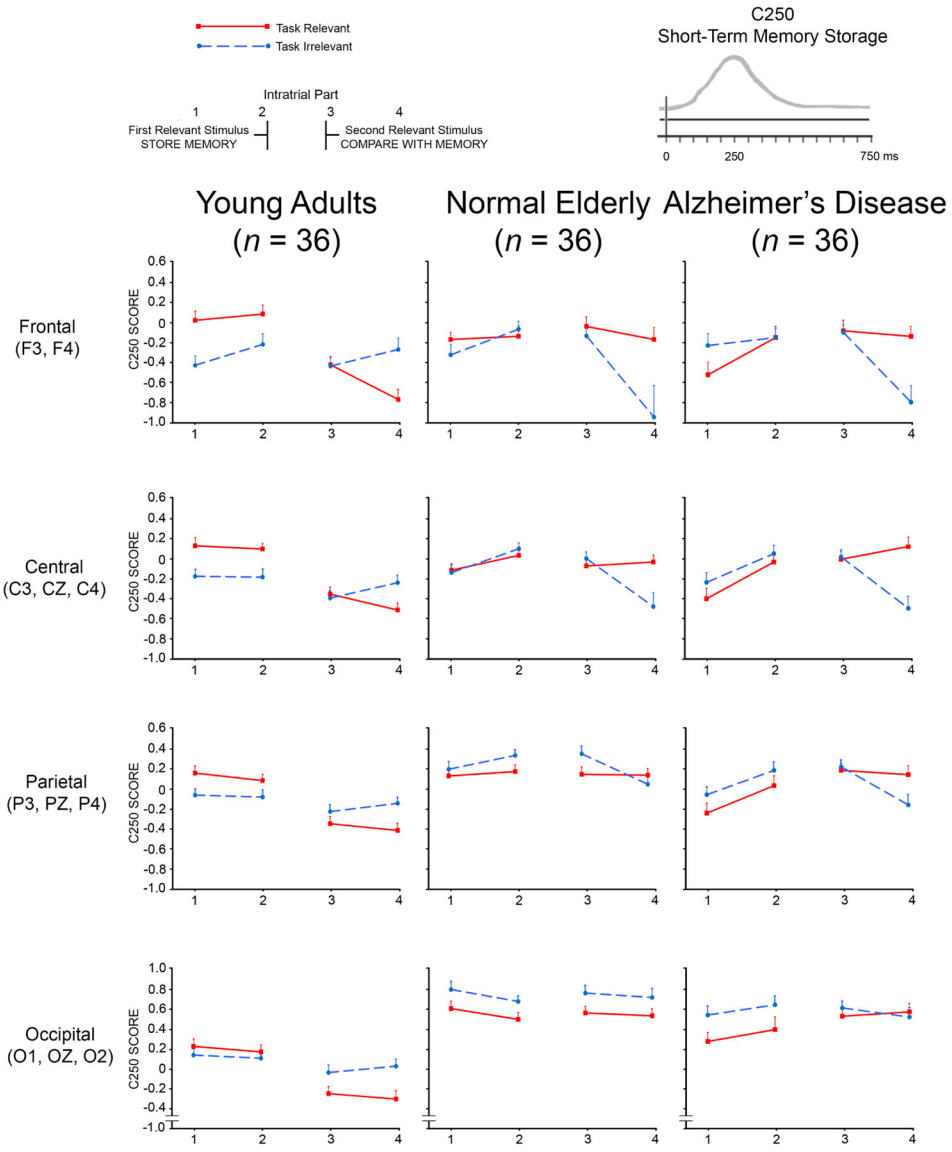

Figure 4.

The C250 "memory storage" ERP component as a function of Number-Letter task effects for the Young Adult, Normal Elderly, and AD groups for brain regions of interest. The Young Adult group showed the most prominent differentiation between relevant and irrelevant stimuli in parts 1 and 2, when memory storage of the first relevant stimulus is key to successfully performing the Number-Letter task. The Normal Elderly and AD groups demonstrated the most prominent differentiation between relevant and irrelevant stimuli in part 4. Their responses also increased, anterior to posterior, to a greater extent than in the Young Adult group (note the different range in the Occipital region graphs). Error bars represent SEM.

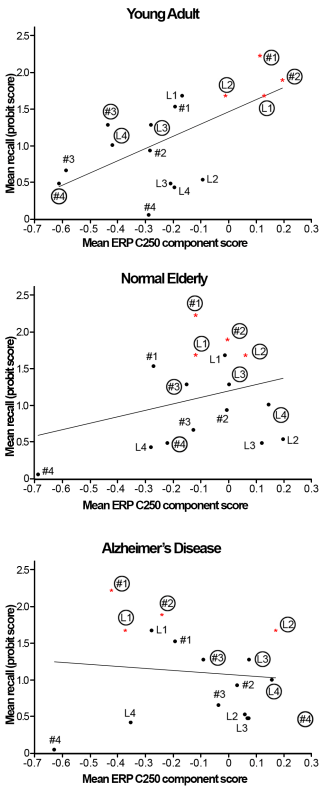

Figure 5.

Correlations for each task condition between behavioral probe recall data from an independent Young Adult group and brain ERP C250 scores at the central brain region (average of C3, CZ, and C4) for the sixteen Number-Letter conditions. Each task condition is denoted by a symbol composed of a Stimulus Type, an Intratrial Part, and its Relevancy. L = Letters. # = Numbers. 1–4 = Intratrial parts. Circled symbols are task relevant. Red dots indicate relevant numbers and letters in parts 1 or 2 (memory storage required). The present Young Adult group showed a positive, significant correlation between C250 and memory probe data, suggesting that C250 amplitudes were increased for stimuli that required memory storage. The Normal Elderly group exhibited a weaker relationship, indicating that irrelevant stimuli and relevant stimuli that do not require storage actually elicited higher C250 amplitudes than they did in the Young Adult group. The AD showed essentially no correlation.

Table 1

Demographical, neuropsychological, and behavioral results for Young Adult, Normal Elderly, and early-stage AD groups.

Group	Age	Education	MMSE[a]	% Correct[b]
Young Adult *(n = 36)*	21.8 (1.6)	15.4 (1.1)	29.5 (0.8)	98.0 (2.1)
Normal Elderly *(n=36)*	74.2 (7.1)	15.5 (2.4)	29.1 (0.9)	98.3 (1.7)
AD *(n=36)*	74.9 (7.4)	14.4 (2.9)	24.6 (2.7)	86.8 (11.3)

Note. Values appear as mean (SD). The age and education information is in number of years. Both the AD and Normal Elderly groups contained 18 women and 18 men, totaling 36 subjects in each group. The Young Adult group contained 22 women and 14 men.

[a]MMSE = Mini-Mental State Examination (Folstein, Folstein and McHugh, 1975) (maximum of 30 points).

[b]Number of correctly answered trials divided by the total number of trials (204) in our Number-Letter paradigm. Only correct trials were used in subsequent ERP analyses

Table 2

C250 memory storage effects for each of the three subject groups at the frontal, central, parietal, and occipital regions. Descriptive statistics appear as Mean (SEM) of C250 component scores of each Intratrial Part in the Relevant and Irrelevant columns. Stimulus Type is averaged in this analysis. Significant Relevancy X Part interactions for each group at each region are broken down by testing the Relevancy effect for each Intratrial Part. Significant effects are marked in bold. This is the model of memory storage in our task: short-term storage of a stimulus is influenced by both its position in the sequence of the trial and its relevance to the task.

A. Young Adults						
	Relevant	**Irrelevant**	**df**	***F***	***p***	***Partial η²***
			Frontal			
Part 1	0.03 (0.14)	−0.42 (0.17)	1, 35	**11.26**	**0.0019**	**0.24**
Part 2	0.09 (0.19)	−0.21 (0.14)	1, 35	**5.32**	**0.03**	**0.13**
Part 3	−0.41 (0.14)	−0.43 (0.13)	1, 35	0.01	0.91	0.0
Part 4	−0.76 (0.16)	−0.26 (0.13)	1, 35	**10.44**	**0.003**	**0.23**
			Central			
Part 1	0.12 (0.10)	−0.18 (0.14)	1, 35	**7.62**	**0.009**	**0.18**
Part 2	0.09 (0.14)	−0.19 (0.12)	1, 35	**6.75**	**0.01**	**0.16**
Part 3	−0.36 (0.13)	−0.40 (0.11)	1, 35	0.15	0.70	0.00
Part 4	−0.52 (0.13)	−0.24 (0.11)	1, 35	**5.72**	**0.02**	**0.14**
			Parietal			
Part 1	0.15 (0.09)	−0.07 (0.12)	1, 35	**4.55**	**0.04**	**0.11**
Part 2	0.08 (0.12)	−0.09 (0.12)	1, 35	2.85	0.10	0.07
Part 3	−0.35 (0.13)	−0.23 (0.10)	1, 35	1.25	0.27	0.03
Part 4	−0.42 (0.12)	−0.15 (0.11)	1, 35	**6.65**	**0.01**	**0.16**
			Occipital			
Part 1	0.23 (0.10)	0.14 (0.12)	1, 35	0.80	0.38	0.02
Part 2	0.17 (0.12)	0.11 (0.12)	1, 35	0.59	0.45	0.02
Part 3	−0.25 (0.13)	−0.04 (0.11)	1, 35	**4.09**	**0.05**	**0.10**

Part 4	−0.30 (0.13)	0.03 (0.13)	1, 35	**8.73**	**0.006**	**0.20**

B. Normal Elderly

	Relevant	Irrelevant	df	*F*	*p*	*Partial* η^2
			Frontal			
Part 1	−0.18 (0.16)	−0.33 (0.19)	1, 35	2.71	0.11	0.07
Part 2	−0.15 (0.14)	−0.08 (0.14)	1, 35	0.45	0.50	0.01
Part 3	−0.05 (0.14)	−0.14 (0.13)	1, 35	0.86	0.36	0.02
Part 4	−0.18 (0.16)	−0.95 (0.35)	1, 35	**4.08**	**0.05**	**0.10**
			Central			
Part 1	−0.12 (0.12)	−0.14 (0.14)	1, 35	0.12	0.72	0.00
Part 2	0.03 (0.12)	0.10 (0.11)	1, 35	0.42	0.52	0.01
Part 3	−0.07 (0.13)	0.00 (0.12)	1, 35	0.59	0.45	0.02
Part 4	−0.04 (0.12)	−0.48 (0.17)	1, 35	**6.36**	**0.02**	**0.15**
			Parietal			
Part 1	0.12 (0.12)	0.19 (0.14)	—	—	—	—
Part 2	0.17 (0.12)	0.33 (0.10)	—	—	—	—
Part 3	0.14 (0.12)	0.34 (0.13)	—	—	—	—
Part 4	0.14 (0.12)	0.04 (0.13)	—	—	—	—
			Occipital			
Part 1	0.60 (0.16)	0.78 (0.18)	—	—	—	—
Part 2	0.49 (0.15)	0.67 (0.15)	—	—	—	—
Part 3	0.55 (0.17)	0.75 (0.17)	—	—	—	—
Part 4	0.52 (0.18)	0.70 (0.17)	—	—	—	—

C. Alzheimer's Disease

	Relevant	Irrelevant	df	*F*	*p*	*Partial* η^2
			Frontal			
Part 1	−0.52 (0.17)	−0.23 (0.18)	1, 35	2.16	0.15	0.06

Part 2	−0.16 (0.15)	−0.16 (0.09)	1, 35	0.0	1.0	0.0	
Part 3	−0.09 (0.15)	−0.11 (0.14)	1, 35	0.02	0.89	0.0	
Part 4	−0.15 (0.16)	−0.80 (0.20)	1, 35	**9.14**	**0.005**	**0.21**	
			Central				
Part 1	−0.40 (0.16)	−0.24 (0.17)	1, 35	1.12	0.30	0.03	
Part 2	−0.04 (0.15)	0.04 (0.12)	1, 35	0.43	0.52	0.01	
Part 3	−0.01 (0.14)	0.01 (0.14)	1, 35	0.07	0.79	0.00	
Part 4	0.11 (0.14)	−0.50 (0.15)	1, 35	**13.10**	**0.0009**	**0.27**	
			Parietal				
Part 1	−0.25 (0.15)	−0.06 (0.12)	1, 35	2.59	0.12	0.07	
Part 2	0.03 (0.14)	0.18 (0.12)	1, 35	1.60	0.21	0.04	
Part 3	0.18 (0.10)	0.22 (0.11)	1, 35	0.14	0.71	0.00	
Part 4	0.14 (0.13)	−0.17 (0.14)	1, 35	3.72	0.06	0.10	
			Occipital				
Part 1	0.27 (0.14)	0.53 (0.11)	—	—	—	—	
Part 2	0.39 (0.16)	0.64 (0.13)	—	—	—	—	
Part 3	0.52 (0.15)	0.61 (0.11)	—	—	—	—	
Part 4	0.57 (0.11)	0.51 (0.12)	—	—	—	—	