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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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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.

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.
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.

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).

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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 et al., 1978a, 1981; Friedman et al., 1978; Ruchkin et al., 1990; Begleiter et al., 1993; Polich, 2007; Rugg and Curran, 2007; Fukuda et al., 2010), recognition and familiarity (Pfütze et al., 2002; Trenner et al., 2004; Morgan et al., 2008), semantic meaning (Chapman et al., 1978b), 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, 2011; Missonnier et al., 2007; Rossini et al., 2007; Jackson and Snyder, 2008; Olichney et al., 2008; Cespón et al., 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 et al., 1978a, 1981, 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, 2011), and P600 or Late Positive Component (Olichney et al., 2008, 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, 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, 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 et al., 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

[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, $\eta_p^2 = 0.06$).