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Research Report

Brain source localization of MMN, P300 and N400: Aging and gender differences

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The localization of neuronal generators during an ERP study, using a high-density electroencephalogram (HD-EEG) equipment was made on three Evoked Related Potential (ERP) components, i.e., the Mismatch Negativity (MMN), the P300 and the N400. Furthermore, the ERP characteristics, their field distribution and the area of their maximum field intensity were extracted and compared between young and elderly, as well as between females and males. A two tone oddball experiment was conducted, involving 27 young adults and 18 elderly, healthy and right handed, and HD-EEG data were acquired. These data were then subjected to auditory ERPs extraction and thorough statistical analysis. The derived experimental results revealed significant age-related differences to both the latencies and the amplitudes of the MMN and the P300 and the topographic distribution of the HD-EEG amplitudes. Additionally, a shift in the maximum intensities from frontal to temporal lobe with aging appeared in the case of the P300, whereas no effect was observed for the MMN component. No statistical significant differences ($p > 0.05$) due to age was found in N400 characteristics. Finally, gender-related differences were significant in the response time of the subjects, finding males response faster. The level and the location of the maximum intensity of sources also differed between genders, especially in young subjects. These findings justify the enhanced potential of HD-EEG data to accurately reflect the age and gender dependencies at the three components of simple auditory ERPs and pave the way for the investigation of neurodegenerative pathologies, such as the Alzheimer's disease.

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1. Introduction

Electroencephalogram (EEG) provides a non-invasive assessment of cortical activity. Developments in both EEG acquisition technology and data processing have made possible the identification and characterization of specific deflections comprising the activity associated with a given experimental stimulus or response. This stimulus can be auditory, visual, tactile, olfactory or even gustatory. Event Related Potential (ERP) is a time locked measure of electrical activity of the cerebral surface, representing a distinct phase of cortical processing, by means of signal averaging (Patel and Azzam, 2005). ERPs are a very useful tool to study cognitive processes such as the reception and processing of sensory information, selective attention, memory updating, semantic comprehension, and cognitive processes disturbances as well, non invasively and with high temporal analysis (Duncan et al., 2009; Goodin, 1990; Pang et al., 1990; Polich et al., 1986). The most well known ERPs have a characteristic waveform with clearly identifiable components named after their polarity and approximate latency (e.g., P100, N100, P200, N200, P300, N400).

Aging effect on the healthy human brain has been studied extensively with neuropsychological (Dahlin et al., 2008; Johnson et al., 2013; Li et al., 2008; Manenti et al., 2013), neuroimaging (Maillet and Rajah, 2013; Steffener et al., 2014), and neurophysiological studies (Anderer, 2003; Harris et al., 2012; Zöllig et al., 2007). All these studies confirm a shift of cognitive processes, including slowing in the rate of mental processing speed (Harris et al., 2012), neurophysiological, volumetric and, even functional connectivity measures. It has been a controversial issue whether this slowing is generalized or process specific. ERPs have been widely used to study the impact of age on the healthy human brain (Anderer, 2003; Harris et al., 2012; Juckel et al., 2012; Kerr et al., 2010; Nessler et al., 2008; Stothart et al., 2013; Walhovd et al., 2008). Some studies support that stimulus encoding and feature extraction become longer in elderly (Madden and Allen, 1991; Madden, 1988), whereas others suggest that response processes, such as response selection, initiation and execution are slowed (Pratt et al., 1989). Other studies confirm an age-related decrease in speed of information processing, in general (Madden, 1992; Salthouse, 2000), although numerous existing data support the opposite (Becic et al., 2007; Bucur et al., 2005). Recent data suggest that is also task specific (Bashore et al., 2013; Smulders et al., 1999) and it is more obvious when a stimulus input is followed by a response output (Bashore et al., 2013).

Gender effects are also observed on the healthy human brain. Cognitive task performance present significant differences between genders (Ingalhalikar et al., 2014; Satterthwaite et al., 2014b). ERP studies using the oddball task as stimuli also documented the gender effect (Karakaş et al., 2006), while using emotional stimuli present even more pronounced gender effect (Arnone et al., 2011; Hung and Cheng, 2014; Proverbio et al., 2010). Inconsistently, the opposing statement supporting that there are no gender differences in the ERP components has been also reported (Fallgatter et al., 1999; Kasai et al., 2002).

In the present study, the age and gender related differences of the three late ERP components, i.e., MMN, P300 and N400 elicited by a classic two sound active oddball paradigm are examined. The oddball paradigm is a method used in ERP research in which trains of stimuli that are usually auditory or visual are used to assess the neural reactions to unpredictable, yet recognizable events. The subject is asked to identify the target stimulus from common background stimulus either by counting or by button pressing (Squires et al., 1975). High density EEG signals (256 channels) are recorded in an attempt to capture as much information as possible. The sLORETA is employed to extract the brain sources and investigate on the effect of aging and gender on the distribution of the activated areas.

1.1. *Mismatch negativity (MMN)*

The mismatch negativity MMN or auditory N2a is a frontocentral negativity of approximate 0.5–5 μV in amplitude that appears in the latency range of 100–250 ms (Duncan et al., 2009). MMN is elicited in a task-independent manner by auditory oddball detection paradigms. Infrequent "*target*" sounds occurring in a sequence of repetitive "*standard*" sounds elicit this event-related brain potential response, even in the absence of attention to these sounds. MMN appears to be caused by a neuronal mismatch between the target stimuli and a sensory-memory trace representing the standard stimuli (Kujala et al., 2007). Since the MMN is generated regardless of attention to stimuli, it likely represents an automatic cerebral process (Picton et al., 2000). This fact lead to the widespread use of MMN when investigating patients with communication or attention problems (Ilvonen et al., 2004; Luauté et al., 2005), as well as, children and infants (Winkler et al., 2003), even fetuses (Huotilainen et al., 2001). The main intra-cerebral sources for the MMN are located in the auditory cortices of the temporal lobe (Picton et al., 2000). However it is also described a frontal-lobe involvement in MMN generation, perhaps due to the involuntary switching of attention when the target sound appears. In addition, MMN generators have been reported in the parietal lobe (Lavikainen et al., 1994) and sub-cortical, as well (Csépe, 1995), with thalamic and hippocampal generation of possible MMN subcomponents (Duncan et al., 2009). The MMN is clinically helpful in terms of demonstrating disordered sensory processing or disordered memory in groups of patients (Kujala et al., 2007; Picton et al., 2000).

In studies of aging, MMN has been used to assess the duration of auditory sensory-memory traces (Pekkonen et al., 1996). This duration in young adults is approximately of 5–10 s, whereas in older decreases gradually. This outcome is thought to reflect a general age-related decrease in brain plasticity (Duncan et al., 2009). Research data suggest that MMN peak areas decrease in the older population, suggesting a shortening of the sensory auditory memory trace when high (3 to 8 s) inter-stimulus intervals (ISIs) are used (Pekkonen et al., 1996). However, in a similar oddball paradigm, having changed only the ISIs to shorter ones, MMN latency and amplitude varied little as a result of increasing age (Patel and Azzam, 2005).