AGING-ASSOCIATED CHANGES IN AUDITORY EVENT-RELATED POTENTIALS AND THEIR CORRELATION TO NEUROPSYCHOLOGICAL MEASURES

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Aging is related to changes in both sensory processing and cognitive functioning. The neural activation of cognitive and sensory processes in the brain is often investigated with event-related potentials (ERP) elicited in electroencephalography (EEG). Whereas auditory processing as measured by ERPs and its relationship to cognitive abilities has been studied, there are only few investigations comparing young and elderly adults. To this end, ERPs to auditory stimuli and a set of cognitive tests were examined in young (N = 41) and elderly (N = 43) participants. The study employed the oddball stimulus paradigm in which the mismatch negativity (MMN), a memory-based response to automatic change detection is elicited. Here MMN was applied to measure brain's ability to detect changes in sound frequency and it was assumed that amplitude modulation of the MMN in the group of elderly would indicate the cognitive decline in this group. Auditory MMN was investigated in a passive oddball paradigm in which frequently presented standard tones were rarely and randomly replaced by a deviant tone of different frequency. As expected, the stimuli evoked MMN and an attention-related P2 response. Both MMN and P2 responses were attenuated in aged compared to young. Additionally, the ERPs and cognitive test scores were correlated in the group of elderly participants. The strongest correlations were between errors made in the Stroop task and MMN. The results suggest that cognitive decline is prevalent also in healthy, normal aging.

Keywords: aging, auditory change detection, cognitive tests, electroencephalography (EEG), event-related potential (ERP), mismatch negativity (MMN)

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KIRJAVAINEN, VILLE: Ikääntymiseen liittyvät muutokset auditiivisissa herätevasteissa ja niiden yhteys neuropsykologisiin testeihin

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Ikääntyminen on yhteydessä muutoksiin sekä aistinvaraisessa prosessoinnissa että kognitiivisessa toiminnassa. Kognitiivisten ja aistinvaraisten tapahtumien hermostollista aktivaatiota aivoissa usein tutkitaan herätevasteilla elektroenkefalografiamenetelmällä. Vaikka äänien prosessointia ja sen yhteyttä kognitiivisiin kykyihin on aikaisemmin tutkittu, nuorten ja ikääntyneiden vertailua käsittäviä tutkimuksia on hyvin vähän. Tässä tutkimuksessa tarkasteltiin herätevasteita auditiivisiin ärsykkeisiin ja kognitiivisia testejä nuorilla (N = 41) ja ikääntyneillä (N = 43) osallistujilla. Tutkimus hyödynsi poikkeavuusnegatiivisuutta, joka on muistipohjainen vaste automaattiseen muutoksenhavaitsemiseen. Poikkeavuusnegatiivisuutta käytettiin mitattaessa aivojen kykyä havaita muutoksia äänitaajuuksissa, ja oletettiin, että ikääntyneillä voimakkuuden muutokset viittaisivat kognitiiviseen heikkenemiseen. Kuuloaistiin liittyvää poikkeavuusnegatiivisuutta tutkittiin koeasetelmassa, jossa tutkittava ei kiinnittänyt huomiota ääniärsykkeisiin ja osa ärsykkeistä oli poikkeavia taajuudeltaan. Usein esitetyt toistuvat ärsykkeet korvattiin harvoin ja satunnaisesti taajuudeltaan poikkeavilla ärsykkeillä. Kuten oletettiin, esitetyt ärsykkeet saivat aikaan poikkeavuusnegatiivisuusvasteita ja tarkkaavuuteen liittyviä P2-vasteita. Sekä poikkeavuusnegatiivisuusvasteet että P2-vasteet ääniin olivat ikääntyneillä matalampia voimakkuudeltaan verrattuna nuoriin. Myös, ikääntyneiden kognitiivisten testien tuloksia verrattiin heidän poikkeavuusnegatiivisuusvasteiden voimakkuuksiin. Voimakkaimmat korrelaatiot olivat Stroop-testissä tehtyjen virheiden ja poikkeavuusnegatiivisuuden välillä. Löydökset viittaavat siihen, että kognitiivinen heikkeneminen on yleistä myös terveillä, tyypillisesti ikääntyvillä.

Avainsanat: auditiivinen muutoksenhavaitseminen, elektroenkefalografia, herätevaste, ikääntyminen, kognitiiviset testit, poikkeavuusnegatiivisuus

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INTRODUCTION

The number of elderly population is growing. In Finland alone, between 2000 and 2030 the number of individuals over 65 years old will increase over 75 % (Nivalainen & Volk, 2002). Reduction of working aged population has effects on a national level, such as need for higher taxation. Furthermore, the sheer volume of elderly in need of some form of assistance has major implications towards the expenses needed to invest in public health. Moreover, cognitive functioning and wellbeing are becoming increasingly important in society, as in 2030 one out of four Finnish will be over 65 years of age (Nivalainen & Volk, 2002). Therefore, the importance of studying aging grows progressively along with the level of aging population. Yet, a large number of researches focus on neurological disorders related to aging, whereas there is a growing concern over the typically aging; the population growth should also accentuate research of healthy individuals, who are affected more so of physiological aging.

Generally, aging is associated with cognitive decline. In terms of studying this aspect of wellbeing, the current technology allows for brain imaging along with traditional cognitive tests. By means of brain imaging methods, such as electroencephalography (EEG), one is able to understand the relationship between the changes in neural and cognitive functioning. The fast temporal accuracy of EEG enables detailed inspection of age-related changes with uncomplicated experimental setups. One common measure of cognitive decline is mismatch negativity.

Mismatch negativity

Mismatch negativity (MMN) is an event-related potential (ERP), which is elicited when a deviant stimulus disrupts a pattern formed by frequently presented standard stimuli. MMN was discovered in 1978 (Näätänen, Gaillard, & Mäntysalo, 1978), and it has been studied actively to this day. MMN is an automatic, early ERP detectable with brain imaging methods, such as EEG and magnetoencephalography. MMN is determined by the difference between the deviant and standard stimuli, most noticeable in temporal and frontal brain regions (Sams, Paavilainen, Alho, & Näätänen, 1985). Additionally, MMN can be recorded in various animals: monkeys (Javitt, Schroeder, Steinschneider, Arezzo, & Vaughan, 1992), rats (Astikainen, Ruusuvirta, Wikgren, & Penttonen,

2006), cats (Pincze, Lakatos, Rajkai, Ulbert, & Karmos, 2002), guinea pigs (Kraus, McGee, Littman, Nicol, & King, 1994), rabbits (Astikainen, Ruusuvirta, & Korhonen, 2005) and mice (Ehrlichman et al., 2009). It has been established in several sensory modalities: somatosensory (Kekoni et al., 1997), visual (Alho, Woods, Algazi, & Näätänen, 1992; Astikainen, Ruusuvirta, & Korhonen, 2001) and olfactory (Krauel, Schott, Sojka, Pause, & Ferstl, 1999). However, the research has been most prominent in the auditory domain.

MMN represents brain's automatic change detection mechanism. MMN elicitation does not depend on attention, and is most commonly recorded in a non-attentive state (also known as an ignore condition). Indeed, MMN can be obtained from, for example, anesthetized rats (Ruusuvirta, Koivisto, Wikgren, & Astikainen, 2007) and comatose patients (Fischer et al., 1999). A condition where participant does not pay attention to ongoing stimuli provides data with less interference from non-substantial attentional sources (Näätänen, Kujala, & Winkler, 2011). Granting, tenacious focus outside the experimental stimuli can be disadvantageous in MMN research setting, as it can attenuate MMN amplitude (Müller, Achenbach, Oades, Bender, & Schall, 2002; Woldorff, Hackley, & Hillyard, 1991).

Auditory ERPs in an ignore condition

In auditory modality, MMN is regarded as the sole indicator of hearing's temporal accuracy (Näätänen, 2000). MMNs appear at different latencies depending on the modality. Auditory MMN (aMMN) peaks typically between 100 and 250 milliseconds post-stimulus. There are several ways to produce aMMN; one can manipulate, for example, the intensity, stimulus-onset asynchrony (SOA) inter-stimulus interval (ISI), duration, frequency or silent gap of the stimuli. Moreover, since aMMN is generated by deviance in an established pattern, standard stimulus can comprise of numerous elements instead of one (Näätänen, Astikainen, Ruusuvirta, & Huotilainen, 2010). Thus, deviance can be elicited by an irregularity in a sequence of tonal sounds. Albeit there is abundance of means to produce aMMN, frequency or duration are the most common deviants conducted in research.

MMN is preceded by N1, a deflection of negative polarity that appears approximately 100 milliseconds after stimulus-onset (Näätänen & Picton, 1987). Similarly to the MMN it emerges regardless of attention, thus it has been regarded to be an obligatory response (Hämäläinen, Fosker, Szücs, & Goswami, 2011).

P2 is a positive ERP response, typically reported at 150-250 ms, later latencies being more common in oddball experimental settings (García-Larrea, Lukaszewicz, & Mauguière, 1992). P2 assists events related to sensory processing, and has been described often in association to N1 as a N1-P2 deflection, where the negative N1 is followed by positive P2. In addition, P2 is linked to cognitive functions as a higher-order perceptual process (Evans & Federmeier, 2007). Moreover, it has been seen as a prerequisite to P300, essential ERP response in decision-making (Dempster, 1991; Dempster, 1992).

Aging and auditory ERPs

Along with age, capability to maintain new knowledge and learn skills is decreased, possibly due to slower neural processing of information (Adams & Victor, 1989; Luszcz & Bryan, 1998). Moreover, there are structural changes related to aging, as brain volume decreases and cortical sulci enlarge (Dennis & Cabeza, 2008). Attenuation of aMMN has been shown to correspond with several disorders, such as Alzheimer's disease, HIV, dementia and Parkinson's disease (Näätänen et al., 2012). Yet, the attenuation of aMMN arises also due to typical aging (Gaeta, Friedman, Ritter, & Cheng, 2001). For example, Kiang et al.'s (Kiang, Braff, Sprock, & Light, 2009) study with 147 participants indicated to a clear relationship between age and aMMN as the aMMN amplitude decreased the older the participants were. However, according to Cheng et al.´s review (2013) of aging's impact on MMN all the findings do not concur. After excluding from the review considerable amount of the research articles (due to active condition, insufficient reports on means and standard deviations, untraditional oddball experiment, etc.), Cheng et al. were left with twelve experiments; nine experiments displayed a significant correlation between aging and aMMN, whereas three found no significant diminishing of amplitude. The properties of the deviance could alter the outcomes.

For instance, of the experiments Cheng et al. inspected, seven had used frequency as deviant and five of those unambiguously found aMMN attenuation in aging (Alain & Woods, 1999; Cooper, Todd, McGill, & Michie, 2006; Gaeta, Friedman, Ritter, & Cheng, 1998; Horvath, Czigler, Winkler, & Teder-Saelejaervi, 2007; Schiff et al., 2008). One had no differences between young and old participants (Mueller, Brehmer, von Oertzen, Li, & Lindenberger, 2008) and another had no significant aMMN reduction when SOA was 0.5 or 1 second, but did when SOA was 4.5 seconds (Pekkonen et al., 1996). Indeed, when the deviance of the stimuli is manipulated with SOA or ISI, shorter delay between stimuli does not always affect the MMN, whereas longer delay does (Cooper et al., 2006; Pekkonen, Jousmäki, Partanen, & Karhu, 1993; Ruzzoli, Pirulli, Brignani, Maioli, & Miniussi, 2012). In addition,

Schroeder et al. (1995) gathered that compared with the young, low-functioning elderly had reduced aMMN, while the aMMN of high-functioning elderly remained unchanged. Nonetheless, although Cooper and colleagues (2006) found the length of the SOA considerable, the aMMN attenuation was found with shorter SOA's as well. Allowing for the relevance of the length of ISI on MMN strength, Pekkonen (2000) deduced that MMN also assesses the length of stimulus trace in the modality domain.

Regarding P2 modulation in amplitude and latency in aging, the evidence is inconclusive. While there have been findings where P2 amplitude increases along with age (Amenedo & Díaz, 1998; Amenedo & Diaz, 1999), others have found it to be not affected by age (Barrett, Neshige, & Shibasaki, 1987; Brown, Marsh, & LaRue, 1983), and one study concluded P2 to decrease with age (Czigler, Csibra, & Csontos, 1992). In terms of P2 latency and aging, some studies have found P2 to be unaffected by advancing age whereas a few have found the latency to increase (Goodin, Squires, Henderson, & Starr, 1978; Iragui, Kutas, Mitchiner, & Hillyard, 1993) and some findings indicate to the latency no be unchanged (Amenedo & Díaz, 1998; Amenedo & Diaz, 1999). For a review of P2, see Crowley and Colrain (2004).

Relationship between cognitive tests and MMN

There are some general findings regarding aMMN and cognitive changes. Firstly, altered aMMN has been shown to indicate cognitive deterioration in chronic alcoholism (Polo et al., 2003). Secondly, the cognitive loss for patients with multiple sclerosis has been indexed with aMMN (Jung, Morlet, Mercier, Confavreux, & Fischer, 2006). Thirdly, as cognitive capacity is central in schizophrenia, the cognitive changes have been studied in relation to MMN reasonably well (Kärgel, Sartory, Kariofillis, Wiltfang, & Müller, 2014; Kasai et al., 2002; Toyomaki et al., 2008). Light and Braff (2005) noticed a correspondence with test scores of a comprehensive wellbeing test (Global Assessment of Functioning) and fronto-central aMMN amplitudes in schizophrenia patients. Moreover, the aMMN amplitude was indicative of self-sufficiency in everyday life. In 2007, Light and colleagues established the same connection with a modified version of GAF and aMMN amplitudes, this time with healthy adults. Lastly, Lin et al. (2012) gathered all the studies where correlations were sought between MMN and cognitive tests in schizophrenia research; only one study out of seven had used frequency as a deviant. Only of late, there has been schizophrenia study where MMN and cognitive functions were compared with frequency as deviance (Kärgel et al., 2014). Kärgel et al. found few significant correlations with frequency-deviant, but none with tone-duration. In sum, attenuated MMN amplitude has been shown to

correlate with cognitive tests with varying results, albeit nearly exclusively with tone duration deviance. Nevertheless, in light of this evidence, MMN appears to be a serviceable predictor of cognitive decline.

With respect to studies investigating the relationship of MMN, cognitive tests and aging, there are only two papers published to the best of my knowledge (Foster et al., 2013; Kisley, Davalos, Engleman, Guinther, & Davis, 2005). Mowszowski and colleagues (2012) researched aMMN and cognitive tests, but among two elderly populations: healthy elderly and elderly with mild cognitive impairment. Therefore, the research on the relationship of the MMN and cognitive performance, and the effects of aging to these, is so far sparse.

Kisley (2005) and Foster (2013) identified an association between aMMN and few of the scrutinized cognitive tests. MMN amplitude correlated with Ray Auditory Verbal Learning Test (RAVLT) and Tower of London (TOL) task in both studies, and with a conditional reaction time task in Kisley's and colleagues' study. No significant correlations with aMMN latency were established. In a sense, Foster et al. carried on where Kisley et al. left; Kisley's group used a subsample of the participants in order to compare cognitive tests and aMMN and didn't take into consideration demographic variables. Foster et al. criticized these actions and took them into account. Perhaps prematurely, Cheng and colleagues (2013) drew wide-ranging conclusions on strength of pre-attentive aMMN based on these findings. However, one essential item was not altered: the type of deviance. The two had ISI as a manner of deviance. Thus, there are no studies of MMN, cognitive tests and aging with any other type of deviant stimuli.

Since aMMN was found originally with simple frequency deviations, it is peculiar that frequency wasn't first and foremost choice of deviance for Kisley's or Foster's research groups. The present study incorporates frequency as deviant stimuli, presenting unique perspective to research concerning MMN, aging and cognitive tests.

Aims of the study

The present study investigated whether the frequency deviant changes in sounds elicit MMN and possibly also P2 similarly in the groups of young and elderly adults. We expected to find a robust MMN in young participants, but assumed attenuation in its amplitude in aged. In addition, the correlations between ERP amplitudes and cognitive tests were examined among aged. Founding upon

the findings of Kisley et al. (Kisley et al., 2005) and Foster et al. (Foster et al., 2013), we expected a positive relationship between MMN amplitude and tests assessing frontal lobe functioning (executive functions). P2 and cognitive tests were investigated with an interest towards changes in attentional processing.

METHODS

Participants

On the permission of the ethical committee of the University of Jyväskylä, experiments were carried out in between March and June 2013 at the University of Jyväskylä. The present study was part of a physical exercise intervention study for which the elderly were specifically recruited for. The present study compares baseline information of the complete research. Elderly participants were recruited from a lecture at University of the Third Age in Jyväskylä and a Pensioners' Association meeting. Young participants were recruited through University of Jyväskylä's students' association mailing lists and word-of-mouth. A total number of 85 participants took part in the experiment: 41 young female adults aged 20-30 years (mean = 23.7; SD = 2.9) and 43 elderly female adults aged 63-80 (mean = 67.9; SD = 4.4).

Exclusion criteria for all participants included current neuropsychological illnesses, brain operations, pregnancy and left-handedness. Absolute threshold of hearing was tested at 500 and 1000 Hz (mean = 21.1 dB sound pressure level (SPL); SD = 11.6 dB SPL; range = 4-59 dB SPL). 750 Hz frequency, which was a presented auditory tone in the EEG tasks, was not tested due to the lack of such feature in the hearing testing device. Participants completed cognitive tests and EEG tasks, which lasted approximately three hours in total. All participants received either a movie ticket or a bag of coffee upon completion of the session.

EEG recording and auditory stimuli

During the recording, the participant was seated to a chair in an electrically shielded, dimly lit room. During the auditory task, the participant watched a silent movie. The movie was without captions in

order to increase the engagement to the film. The distance between the monitor and the participant was approximately 1.5 meters. Briefing included a notion that the participant should not pay any attention to the auditory stimuli. Participants were instructed to sit relaxed in an armchair avoiding all additional body movement, facial expressions, talking and especially excessive head movement.

Participants were informed that they were monitored from the observation room via a video camera concealed above the screen in the experiment room. Furthermore, researchers and participants were able to communicate through an audio setup during the session which was mainly used to give instructions in case of problems during the EEG recordings. Otherwise instructions were given prior to the tasks face to face. Participants had no visual sight to the control room.

The EEG data was recorded using 128-channel EGI Sensor Net (Electrical Geodesics Inc., Hydrogel GSN 128, 1.0). Impedances were kept below 80 kΩ throughout the experiment. Sampling rate was 1000 Hz and data were online filtered from 0.1 to 400 Hz. The vertex electrode (Cz) played the part of the reference electrode.

The auditory stimuli were heard binaurally from a loudspeaker placed 90 cm above the participant. The stimuli were played at 75 dB SPL.

In all stimulus conditions the stimuli were pure sinusoidal sounds. Stimulus-onset asynchrony (SOA) was randomized for 400, 450 or 500 milliseconds. Length of the stimulus was 50 ms. The auditory task consisted of two counterbalanced, non-attentive blocks; in the first block the standard stimulus was 1000 Hz and the deviant 750 Hz, and vice versa in the second block. The oddball paradigm was used to elicit the MMN phenomenon. Each standard stimulus had the random possibility of 86% and deviant of 14% on the requisite of minimum of two standard stimuli before deviant. A total of 1000 stimuli were produced during the task.

Cognitive tests

Cognitive functions were evaluated with thirteen tests before the EEG recording session. Each participant completed all of the tests. Tests were selected in order to encompass a variety of functions which are typically affected by cognitive aging, with emphasis on executive functions and memory. The order of the tests was fixed and designed to maximize the output for each participant. Whole test

set was carried out by a psychologist or a trained research assistant. A single session lasted between 40 and 60 minutes.

Executive functions: The Stroop Color-Word Test (Stroop) is a frontal lobe task, testing executive functions. It consists of three individual tests on separate A4-sheets; the first (Stroop1) comprehends list of colour words written in black. The participant was asked to read out loud all the words. In the second sheet (Stroop2) there are 'Xs' printed in colour, and the participant was asked to name the ink colours. Lastly, the participant was handed a sheet with colour words printed in incongruent colours (Stroop3). The task was to name the colour the word was written in, prompting inhibition to read out loud the written word. All lists were instructed to be read as fast as possible, avoiding mistakes. Moreover, errors made in the tasks were recorded, creating three additional variables for cognitive tests.

Memory: The logical memory task (from Wechsler Memory Scale - Revised) was used to assess immediate and delayed auditive memory, and declarative memory. Participant was told a short story and the participant was asked to repeat it immediately as accurately as possible. Hereupon the recall another story was told, which was followed by its immediate recall. The participant was informed that they would be asked to recall the stories later on. In approximately one hour, in-between EEG-blocks, the participant was asked to repeat the story anew.

Visual reproduction task (from Wechsler Memory Scale - Revised) assesses memory for nonverbal visual stimuli. It includes series of five images, where each is shown for ten seconds. After presentation, the participant was asked to draw the image from memory. In the delayed task, the participant was asked to reproduce the images in no particular order.

Three character recall tasks were completed. The tasks measure the capacity of the working memory. In Digit span task, the participant was told a random sequence of numbers, which were asked to repeat. If the recall was correct, the sequences eventually grew in length. Backward digit span task required the participant to repeat the told sequence in backward order, involving processing of the digits in the working memory. In letter-number task the participant was told sequences which included letters and numbers. The participant was asked to repeat the characters, first numbers in numerical order, from the smallest to the highest, and then letters in alphabetical order.

Attention: Trail Making Test A (TMT-A) assesses basic attention shift. Participant was asked to connect 25 numbers in ascending order on an A4-paper without lifting the pencil.

Trail Making Test B (TMT-B) requires divided attention and working memory. The paper included both numbers and letters. The participant was asked to connect numbers and letters by turns in ascending and alphabetical order.

Both tasks were asked to complete as fast as possible, yet avoiding mistakes. TMTs assess attention and psychomotoric speed. TMT-B is cognitively more demanding and it requires good executive functioning due to the simultaneous processing of two concepts.

Motor speed: The tapping task was conducted in order to assess participant's motor speed and control. In the task, the participant pressed a button on a mechanical tally counter with their thumb. The aim was to tap as many times as possible in a ten second span. The task was completed with the left hand three times consecutively and subsequently with the right hand. The scores for each hand were averaged across the three trials.

Data analysis

BrainVision Analyzer 2.0 software was utilized to analyze the data (Brain Products GmpH). Eye blinks were removed from the data using an algorithm (Gratton, Coles, & Donchin, 1983), and channels with excessive noise and insufficient skin contact were interpolated using spherical spline model (Pernier, Perrin, & Bertrand, 1988). An average from all the channels was used as a new reference. The electrode signals were filtered with 0.1 Hz low cut-off and 20 Hz high cut-off, both with 24 dB/octave roll-off. In addition, a 50 Hz notch filter was applied. 700 ms time windows were extracted stimulus-locked: 200 ms prior to stimulus onset and 500 ms after the stimulus onset. Section between -200 ms and 0 ms served as a baseline. Unusually large variance (outside -100 to 100 μV, peak-to-peak) in EEG data was rejected by default. Furthermore, lowest allowed activity in intervals was set at 0.5 μV. Grand average exports were extracted for both deviant responses and standard responses. One participant was rejected due to insufficient amount of successful segments. Thus, 43 participants were included in the final analysis.

The MMN and P2 deflections arose from the data (Fig. 1). They were established by peak-detection feature in BrainVision Analyzer 2.0. The mean latency for the MMN peak for both aged and young

was 111 ms. Here the deflection is labeled as MMN, but it most probably contains also N1-type activity. The mean latency P2 peak for young was 228 ms, and for aged the P2 peak was 249 ms. The latency for the analysis windows was defined by grand averaged waveforms; a 40-ms time window was centered for the temporal midpoints of the time windows for each group determined from differential responses, in which Global Field Power defined overall activity of electrode clusters. Hence the MMN was 91-131 ms for both age groups, young P2 was 208-248 ms and aged P2 was 229-269 ms. In the analysis, mean amplitudes of the established time windows for each electrode cluster were employed.

Six electrode clusters were formed for the two extracted time windows separately. In consideration of selecting appropriate channels for the time window and age group in question, channels were chosen solely on the activation in voltage maps. Hence the amount of electrodes in each cluster varies. In MMN, the same clustering was applicable for both young and aged: *anterior left* (electrodes 27, 28 and 34 in the EGI Hydrogel GSN 128), *anterior center* (10, 11, 16 and 18), *anterior right* (116, 117 and 123), *posterior left* (64, 65 and 69), *posterior center* (74, 75, 82) and *posterior right* (89, 90 and 95). In P2 time window, the clusters differed between the age groups: *anterior left* (27, 34 and 35 for young; 34, 35, 40 and 41 for aged), *anterior center* (6, 7, 13, 106 and 112 for young; 6, 7, 13, 106 and 112 for aged), *anterior right* (110, 116 and 123 for young; 103, 109, 110 and 116 for aged), *posterior left* (65, 69 and 70 for young; 50, 58 and 64 for aged), *posterior center* (74, 75, 82 for young; 70, 74, 75, 82 and 83 for aged) and *posterior right* (83, 89 and 90 for young; 95, 96 and 101 for aged). See appendices 1, 2 and 3 for figures of clusters.

Statistical analysis

Mean amplitudes from MMN and P2 post-stimulus for six electrode clusters were analyzed in 4-way repeated measures MANOVA [*stimulus type* (standard, deviant) × *anteriority* (anterior, posterior) × *laterality* (left, center, right) × *age group* (young, aged)]. ANOVA was applied to compare differential responses (deviants minus standards) between the age groups whenever *age group* × *stimulus type* effect was found. Paired-samples t-tests were two-tailed. Effect size estimates are described as partial eta squared (η^2_p) scores for MANOVA.

In order to investigate the relationship between cognitive tests and peak values, partial Pearson's correlation coefficients were calculated, controlled for age and hearing. Firstly, the average amplitude information for each channel in the two blocks was averaged, standard and deviant amplitudes

separately. Secondly, the electrodes were clustered based on the strongest activity positions according to voltage maps. Thirdly, the values used for correlations were the differences between the average deviant and standard stimuli in the MMN and P2 time windows. Lastly, all amplitudes were converted to absolute values; thus the reported correlations indicate the effect of the amplitude strength itself on the specific tests rather than to the polarity of the original waveform. Findings were corrected with False Discovery Rate (Benjamini & Hochberg, 1995). Since the focus of the study was in aging, the correlations between cognitive tests and ERP amplitudes were determined only for the aged group.

RESULTS

MMN: 91-131 ms

An interaction effect between stimulus type × anteriority × laterality × age group [$F(2, 81)= 5.70$, $p < 0.005$, $n2p = 0.123$]. The responses to deviants differed from those to standards within young ($t40 = -10.75–10.72$, $p < 0.001$, $d = 1.48–2.20$) and within aged ($t42 = -11.60–10.71$, $p < 0.001$, $d = 1.15–1.62$) at all electrode clusters. MMN was smaller in aged compared to young at *anterior left*, *anterior center*, *posterior left* and *posterior center* [$F(1, 82) = 6.27–9.59$, $p = 0.003–0.014$].

P2: 208-248 ms

An interaction effect between stimulus type × anteriority × laterality × age group [$F(2, 81) = 3.56$, $p = 0.033$, $n2p = 0.081$]. The responses to deviants differed from those to standards within young in five electrode clusters ($t40 = -4.30–4.94$, $p = < 0.001–0.030$, $d = 0.74–1.02$). Responses did not differ in *anterior left* ($p = 0.447$, $d = 0.19$). Within aged responses differed in *anterior right* and *posterior center* ($t42 = -2.12–2.04$, $p = 0.040–0.048$, $d = 0.37–0.43$). Responses did not differ in *anterior left*, *anterior center*, *posterior left* and *posterior right* ($p = 0.065–0.323$, 0.20–0.37). P2 was smaller in aged compared to young at *anterior center* and *posterior right* [$F(1, 82) = 5.65–10.83$, $p = 0.001–0.020$].

Table 1

Cohen's D effect sizes for differences between responses to standard and deviant stimuli in young and aged in MMN and P2

	Young		Aged	
Site	MMN	P2	MMN	P2
Anterior left	**-1.71**	0.19	**-1.45**	0.20
Anterior center	**-2.20**	**1.02**	**-1.60**	0.34
Anterior right	**1.58**	**0.87**	**-1.62**	**0.37**
Posterior left	**2.04**	**-0.74**	**1.42**	-0.20
Posterior center	**1.62**	**-0.83**	**1.16**	**-0.43**
Posterior right	**1.48**	**-0.91**	**1.27**	-0.34

Bolded values represent significant ($p < 0.05$) deviant-standard difference in ANOVA (tables 2 and 3).

Table 2

Mean and standard deviation (SD) of the differential response (deviant-standard) amplitudes for young and aged in MMN with related ANOVA statistics

Site	YOUNG mean amplitude (μV) and SD	AGED mean amplitude (μV) and SD	F	P-values for between-group differences
Anterior left	-1.05 (0.77)	-0.69 (0.54)	6.27	0.014*
Anterior center	-1.88 (1.12)	-1.32 (0.75)	7.26	0.009*
Anterior right	-0.88 (0.67)	-0.85 (0.48)	0.05	0.833
Posterior left	1.41 (0.85)	0.93 (0.57)	9.59	0.003*
Posterior center	1.19 (0.86)	0.78 (0.52)	6.83	0.011*
Posterior right	1.15 (0.87)	0.87 (0.61)	2.84	0.096

*Difference is statistically significant ($p < 0.05$).

Table 3

Mean and standard deviation (SD) of the differential response (deviant-standard) for young and aged in P2 with related ANOVA statistics

Site	YOUNG mean amplitude (μV), and SD	AGED mean amplitude (μV) and SD	F	P-values for between-group differences
Anterior left	0.11 (0.94)	0.11 (0.64)	0.00	0.970
Anterior center	0.99 (1.28)	0.22 (0.81)	10.83	0.001*
Anterior right	0.64 (1.14)	0.23 (0.75)	3.83	0.054
Posterior left	-0.66 (1.35)	-0.18 (1.16)	3.18	0.078
Posterior center	-0.77 (1.40)	-0.38 (1.16)	1.98	0.163
Posterior right	-0.82 (1.22)	-0.26 (0.91)	5.65	0.020*

*Difference is statistically significant ($p < 0.05$).

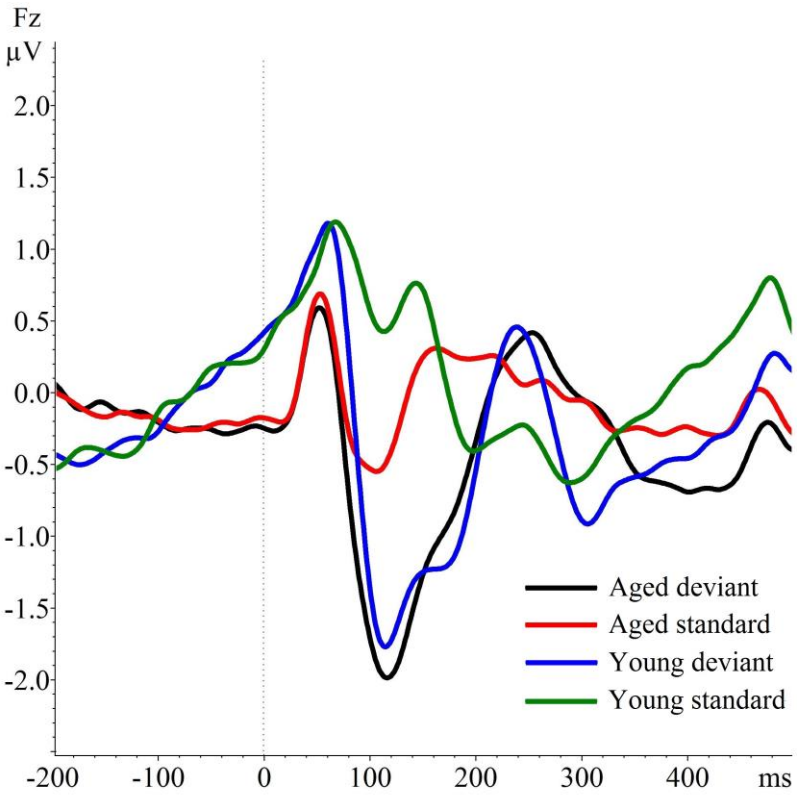

Fig. 1. *Standard and deviant waveforms at Fz (e11) for young and aged*

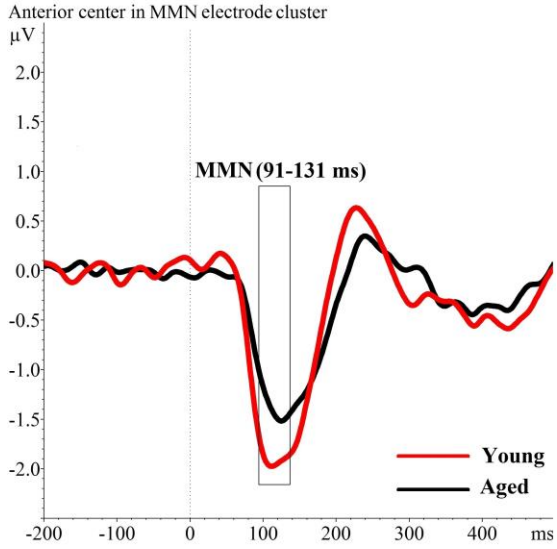

Fig. 2. *Difference waveforms (deviant minus standard responses) at anterior center with optimized electrode clustering for both age groups in MMN*

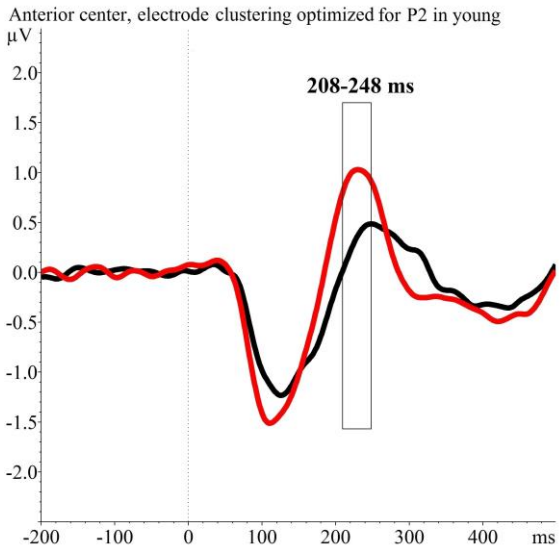

Fig. 3. *Difference waveforms at averaged electrode cluster anterior center with optimized electrode clustering for P2 in young*

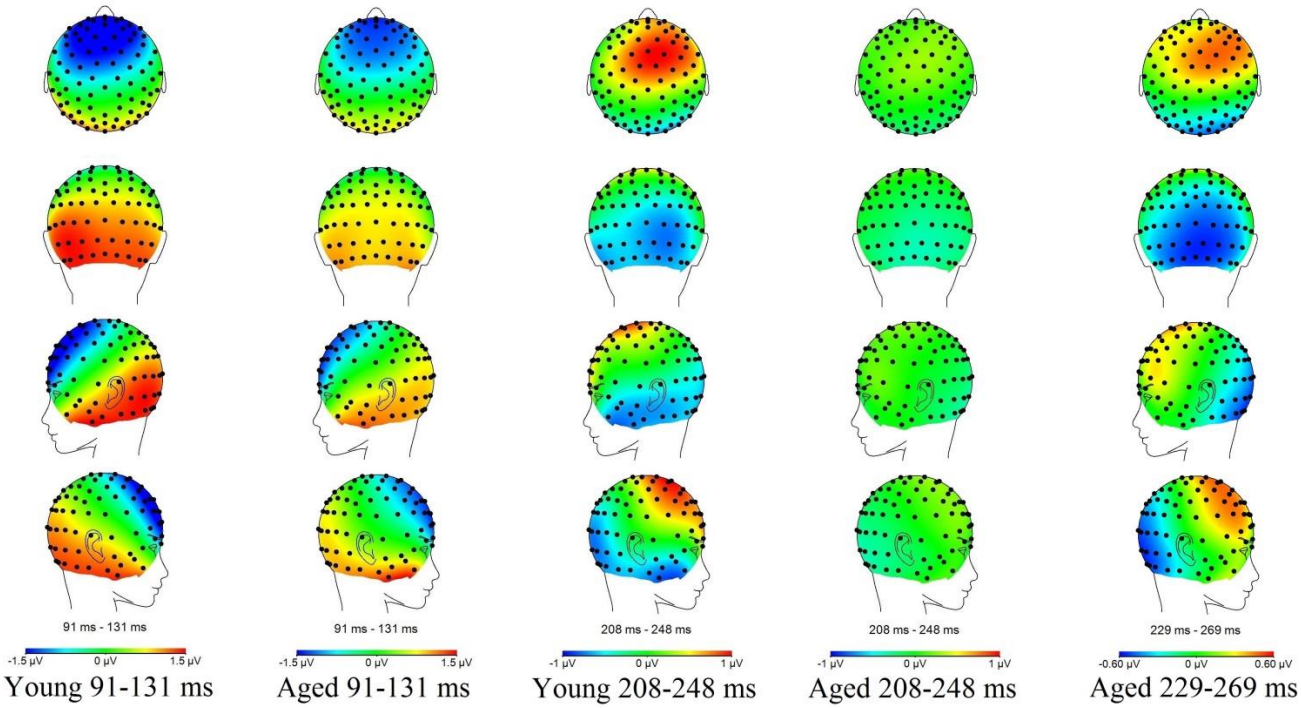

Fig. 4. *Difference wave voltage maps for young and aged at 91-131 ms. Scaling ±1.5 microvolts*

Fig. 5. *Difference wave voltage maps for young and aged at 208-248 ms. Scaling ±1 microvolts*

Fig. 6. Difference wave voltage maps for aged at 229-269 ms. Scaling *±0.6 microvolts*

Correlations between cognitive tests and ERP amplitudes among aged

Table 4

Means and standard deviations for the cognitive test scores in aged, highlighted according to normative values. Normative values are determined for the mean age of the group

	TMTA	TMTB	Logical	Logical delay	Stroop1	Stroop2	Stroop3	Stroop2 errors	Stroop3 errors	Visual
Mean	41.13	88.97	21.44	17.28	55.81	78.53	132.77	0.98	2.58	34.65
SD	13.67	31.49	5.11	5.75	9.39	19.52	30.76	1.37	3.49	4.13

	Visual delay	Digit span	Digit span max	Digit span back	Digit span back_max	Digit-letter	Digit-letter max	Tapping left	Tapping right	Hearing
Mean	31.88	6.84	5.86	6.44	4.63	9.67	5.00	37.47	41.58	21.13
SD	6.00	1.76	1.08	1.58	0.90	2.46	1.20	4.63	5.22	11.60

-3 SD = -2 SD = -1 SD = 0 SD = +1 SD = +2 SD = +3 SD = Not available =

Correlations between all cognitive tests and the six electrode clusters were investigated in the aged group. Table 4 presents the means and standard deviations for all the cognitive tests. In the table's highlighting, the average scores were compared to normative values by using the mean age of the participants in aged group. The standard deviations seem to conform to typical values, between -1 and +1 SD. The test-by-test SD-values are as follows: TMTA +1, TMTB +1, Logical -0.5, Logical delay -0.5, Visual -0.5, Visual delay -0.5, Digit span 0, Digit span back -0.25, Digit-letter +1 SD, Tapping left 0 and Tapping right 0. Normative values for Stroop scores, Digit span max, Digit span back max, Digit-letter max and hearing were not available.

Tables 5 and 6 present all the significant correlations found between cognitive tests and mean amplitudes of MMN and P2 time windows. Due to the large variation in both age and absolute level of hearing in the aged group, both were used as covariates in the partial Pearson's correlation analysis. Absolute levels of threshold for the two frequencies for both ears were averaged in order to provide no more than one variable for hearing. False Discovery Rate correction method was employed in order to decrease the possibility of type I errors. Due to the relatively low number of participants in the aged group (N = 43), the FDR value was set at 0.2. Correlations with p-value below 0.05 are reported here; correlations significant after FDR correction are singled out.

In MMN, *anterior right* and *posterior left* were significantly correlated with the number of errors made in the Stroop3 test after FDR correction (for FDR values in detail, see appendix 4). The interactions are demonstrated in scatterplots, figures 7 and 8.

Although two cognitive variables were correlated with mean amplitudes in P2 with a p-value of less than 0.05, no significant correlations were left after FDR correction (table 6).

Table 5

Summary of significant (p < 0.05) Pearson's correlations of cognitive variables with difference amplitudes in MMN (91-131 ms) among aged (controlled for age and hearing)

		Anterior left	Anterior center	Anterior right	Posterior left	Posterior center	Posterior right
TMTA	Correlation	-.309					
	P-value	.049					
Stroop2 errors	Correlation		.322		.348	.311	
	P-value		.040		.026	.048	
Stroop3 errors	Correlation	.348	.403	.483*	.456*	.390	
	P-value	.026	.009	.001	.003	.012	
Digit-letter	Correlation						.352
	P-value						.024
Digit-letter max	Correlation						.314
	P-value						.046
Tapping right	Correlation		.333	.339			
	P-value		.033	.030			

*Correlation is significant after FDR correction at 0.2.

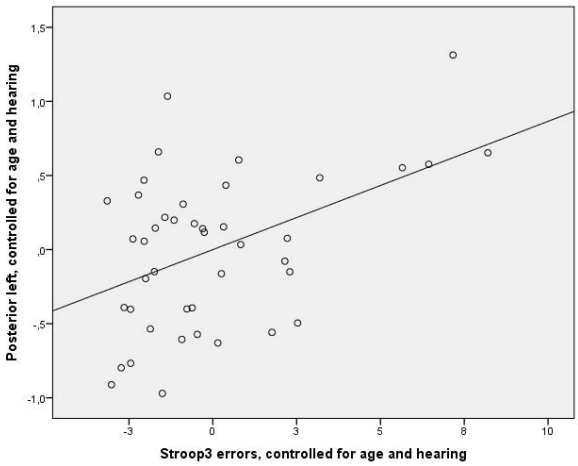

Fig. 7. *Scatterplot for mean amplitude at MMN in posterior left against Stroop3 errors, controlled for age and hearing. Fit line (r = 0.208) indicates trend.*

Fig. 8. *Scatterplot for mean amplitude at MMN in anterior right against Stroop3 errors, controlled for age and hearing. Fit line r = 0.233.*

Table 6

Summary of significant ($p < 0.05$) Pearson's correlations of cognitive variables with difference amplitudes in P2 (229-269 ms) among aged (controlled for age and hearing)

		Anterior left	Anterior center	Anterior right	Posterior left	Posterior center	Posterior right
Stroop2 errors	Correlation			.444			
	P-value			.004			
Tapping left	Correlation					.400	
	P-value					.009	

Neither of the correlations was significant after FDR correction at 0.2.

DISCUSSION

In the current study, MMN was found in young (20-30-year-olds) and aged (over 63-year-olds) groups. The responses to standard and deviant stimuli differed significantly and the amplitude was attenuated in in most of the electrode clusters in aged compared to young. Furthermore, P2 arose in both age groups as expected. In terms of peak amplitudes, P2 was smaller among aged in two electrode clusters. In relation to cognitive tests and ERPs, there were two significant correlations between difference amplitudes in electrode clusters and cognitive variables in MMN time window: Stroop3 errors versus *posterior left* and Stroop3 errors versus *anterior right*. No significant correlations were found between P2 and cognitive tests.

In terms of performance in the cognitive tests, the aged by and large fall in the range of normal variation. Since the participants don't have neuropsychological disorders and the cognitive test scores are typical, the aged could be regarded typically, or normally, aging.

Amplitudes of MMN and P2

The MMN was found in both groups with the frequency deviant. In MMN, the differences in amplitude between responses to standard and deviant stimuli were significant in both age groups at all electrode clusters. In four out of six clusters the aged had attenuated amplitude compared to young. As seen in the figure 4, the type of activation is similar in both age groups, yet slightly lesser in aged. The diminished amplitude in aged agrees with Cheng et al.'s (2013) overall review findings, where the

majority of the researches reported attenuated amplitude in older age groups compared to younger. Furthermore, the MMN reduction was apparent with the application of short SOA (400-500 ms) in the current study, supporting notions of Cooper et al. (2006). Moreover, whereas Schroeder (1995) argued for differences in MMN reduction between high- and low-functioning elderly, the present study demonstrated MMN reduction in normally aging elderly. This provides additional information on the prevalence on MMN attenuation when the aged are cognitively typically functioning.

In MMN the computationally determined peak latency for young and aged was 111 ms; the latency similarity in MMN between age groups was entirely obtained from analysis software, and was not statistically evaluated. For this reason, the outcomes of the latencies can be purely speculative. Bearing this in mind, considering the overall performance in cognitive tests, the cognitive abilities don't seem to affect the MMN latency. Rather, the aging itself could be the most plausible factor. Mowszowski (2012) came to the same conclusion, as individuals with mild cognitive impairment had only attenuation in MMN (no latency differences) in comparison with healthy, age-matched individuals. Mild cognitive impairment, a transitory state towards dementia with major implications to cognitive abilities, did not alter MMN latency. Mowszowski further states that in Alzheimer's disease studies latency differences are not generally found when same age groups are assessed.

The MMN appeared at a similar time interval as the compulsory N1 would be expected. According to responses to standard stimuli in the figure 1 the N1 deflection can be estimated by visual inspection to emerge at circa 100 ms. Yet, since no differentiation between MMN and N1 was applied, the effect of N1 in responses to deviant stimuli is problematic to estimate. However, since the MMN is defined by the difference between responses to standard and deviant stimuli, figure 2 offers an illustrative view of substantial MMN incidence.

In both groups P2 was elicited. Previously P2 amplitude has been found to increase in studies concerning aging, yet the findings have been inconsistent (Crowley & Colrain, 2004). Aged had attenuated responses in two electrode clusters compared to young at 208-248 ms: *anterior center* and *posterior right*. There were no differences in the other four electrode clusters. *Anterior right* and *posterior left* are fairly close to be significant ($p = 0.054$ and $p = 0.078$, respectively); possibly with higher number of participants there would be more significant differences between young and aged P2. This finding is in contrast with some of the previous researches which have found P2 increase along with age (Amenedo & Díaz, 1998, 1999). The attenuation could be related to changes in attentional

processing (Evans & Federmeier, 2007). In the context of P2 as an attentional processing index, the young exhibit more distinctive separation in the earlier time window; at 208-248 ms the young group's responses to deviants differed from those to standards in five electrode clusters. Aged participants' differences were found in two clusters at 208-248 ms. This could relate to later P2 latency in aged.

As retrieved from the peak detection, P2 in young peaks at 228 ms and in aged at 249 ms. Similarly as in the MMN time window, the differences in P2 latencies were not statistically determined. Allowing for this, the delay of 21 ms appears notable, especially when taking into consideration that seems to be virtually no differences in MMN latency between the age groups. The difference is also observable in figure 5, as when the P2 of young is at strongest the difference waves are yet to be seen in voltage maps of aged; there are less deviant-standard differences in aged, which further attests later P2 activation related to aging. Direct comparison of scalp topographies was not performed, yet the visual inspection of P2 provides indications of similar activity between young and aged; P2 in young (208-248 ms) and aged (229-269 ms) appear to be akin in the voltage maps (figures 5 and 6).

The P2 attenuation is particularly noteworthy since the elderly participants in the present study have no neurological disorders and represent typically aging elderly population. Thus the P2 attenuation in aging could be interpreted rather related to normal physiological aging, than to functional impairment. Since the P2 is attenuated, the results give support to the argument of P2 alteration in aging, even if the aged are well-conditioned.

Correlations between cognitive tests and ERP amplitudes

Examination of correlations between cognitive tests to ERP amplitudes is vital as it can provide additional valuable information on aging's effect. Structural and functional changes in the brain are reflected in ERPs, and they are further manifested on behavioural level. These behavioural changes alter cognition which can be measured with cognitive tests. As the present study investigates notably aging, the correlations were done solely for the aged group.

Due to the high number of cognitive tests and electrode clusters, a correction method was necessary for critical observation. FDR takes into account the amount of variables and thus is less prone to reduce true discoveries, unlike some conservative methods, such as Bonferroni correction. Nonetheless, one should bear in mind that same results would have been accomplished if the p-value was set lower. FDR correction was set at 0.2. This is reasonable considering relatively low number of participants in the

aged group. On the other hand, merely two significant correlations were left out of numerous. However, since MMN, aging and cognitive tests haven't been studied earlier with frequency deviations, correlations with $p < 0.05$ were reported in the tables 5 and 6 for further inspection.

Only Stroop3 errors correlated significantly with difference amplitudes in MMN. The direction of the correlation indicates that the more errors in Stroop3, the higher the difference amplitude. In literature, Stroop errors in general are not typically researched, or at least conventionally reported. This might result from the fact that correlations with Stroop3 errors are rarely constructive, since typically not many errors are made. Aged in the current study had an average of 2.6 errors with SD of 3.5 (table 4). In fact, in MMN and cognitive tests only one study has found a correlation between MMN amplitude and Stroop errors (Toyomaki et al., 2008). However, the particular research did not discuss any implications of the finding nor did Toyomaki et al. discuss whether the amplitudes were converted into absolute values, which drastically affects the interpretation. Personal communication with the main author didn't provide further advice on the finding. As it stands, their finding is similar to the one in the present paper. However, instead of focusing solely on the correlation value, the scatterplots of the correlations require some further inspection (figures 7 and 8). The main bodies of correlations do not pool around the fit lines evenly; a few individual values with higher error rate seem to be responsible for the overall high correlation. Scatterplots indicate that the findings might not be as robust as the correlations itself suggests. Pearson correlations are sensitive to single values that agree with the general trend and thus might in numerical form be misleading in terms of the correlational nature of the whole group of findings.

Concerning the rest of the tests, there are only two points of reference (Foster et al., 2013; Kisley et al., 2005) in terms of comparing MMN, aging and cognitive tests. Thus, it is of upmost relevance to note the differences between the aforementioned studies and the current study. Firstly, all the cognitive tests used in the present study and the studies by Kisley et al. (2005) and Foster et al. (2013) were not the same. The current study didn't take into consideration the previous studies when the inclusion of specific tests was made. Tower of London-task wasn't introduced into the current study, whereas it was the test with most significant implications in Kisley's and Foster's groups' findings. The inclusion could have provided insightful investigation, although (in hindsight) the incorporation would have been impossible; Tower of London-task should have been done before and after the intervention in the complete research setting, and the test would have been able to learn, reducing the validity. Tower of

London-task measures executive functioning; it is note-worthy that other tests measuring executive functions didn't yield similar results. Additionally, the Stroop test and TMT-B are understood to represent executive functioning. However, the results regarding Stroop are not unanimous; while Kisley et al. didn't find any relationship between Stroop and MMN amplitude, the current findings indicate that error-prone performance in Stroop is related to greater MMN amplitude. Moreover, TMT-B was not significantly related to MMN in the current study or Kisley et al.'s (2005). Thus, on a theoretical level the comparison of ERP findings and cognitive tests are not coherent. It is plausible, that the cognitive tests do not reflect their functions (i.e. executive functioning) in a purposeful manner. Alternatively, the MMN could arise from a field of cognitive functions which the selected tests did not directly utilize. The tests we consider to assess executive functions may not have similar neurobiological foundation, based on the inconsistency of correlation with tests and MMN amplitude.

Secondly, it should be noted, however, that lack of similar results could be considered a result in itself as it opens up the discussion for the p-value of the deviant stimulus. Regarding the effect on MMN, there are mixed findings; Cheng et al. (2013) argued in their review that estimated effect size is dependent whether the deviant stimulus is frequency (moderate estimated effect size) or duration (large estimated effect size). On the other hand, Pekkonen suggests in his review (2000) that MMN is attenuated when duration is the deviance rather than to frequency deviants within aged population. Perhaps most importantly, there seems to be fundamental differences between duration and frequency deviants according to Foster et al. (2013). They argue that not only duration-deviants activate different brain areas than other deviants, but duration-deviant MMN is as well more accurate in detecting executive dysfunction's abnormal activity. Thus, employing other deviances could result in less successful outcomes.

Thirdly, the current study utilized 128-channel EEG net, while Kisley et al.'s (2005) and Foster et al.'s (2013) studies employed a few disposable electrodes (Fz, Pz, Cz, both mastoids and two under the eyes) of which only Fz was used in analysis for correlations. The limited number of registering electrodes restricts the choice of cognitive tests as it would be futile to employ such tests that do not show any activation in the chosen channels. Foster et al. (2013) acknowledged this and they stated that selection of cognitive tests was influenced by previously found relationship with prefrontal cortex. The current study was more versatile as the high-density net allowed for inspection of all channels and the cognitive tests were incorporated solely due to their relevance to the study, not documented spatial

activation. This approach permitted a less biased set of choices concerning tests choices and observed activation areas. While significant correlations in the present study in the used electrode clusters are few and far between, several low p-value correlations suggest that relationships between MMN amplitudes and cognitive tests should be sought from more than one electrode location.

Lastly, it is worth considering how well cognitive tests and EEG data can be compared. In the end, it is difficult to say if the used measures are accurate enough in order to facilitate all the measured functions or, from a broader point of view, if the current methods in psychometrics are valid for comparison with neural activation. There are numerous tests available, but certain few are commonly selected as indicators of specific cognitive processes. To the best of my knowledge, no systematic comparison of ERP amplitudes and cognitive tests has been made. Therefore, without a strong point of reference, any significant correlation found within the current study could be merely a stroke of luck.

Limitations

When evaluating the results, it should be noted that the participants in the current study were exclusively women. They were mostly from central Finland and both young and aged groups are heavily populated with academic affiliations due to some of the means of recruitment (students' association mailing lists and University of Third Age, respectively). Additionally, as the study was part of an intervention research, the study was likely to attract certain type of volunteers; the participants willing to take part in physical exercise intervention are more likely to be fit in the first place. Thus, the select nature of participants prevents direct comparison of the results to the whole population of the age group. In addition, the hearing threshold test implemented in the current study was fairly crude to fully investigate the relationship between hearing and cognitive tests. The hearing threshold measured on multiple frequencies could prove to be more significant in assessing cognitive tests than many other factors. Since the hearing thresholds vary greatly in the aged group, the stimulus volume could have been adjusted individually. In its present condition, the study had to correct for hearing afterwards in the Pearson correlations, relying on fairly imprecise values from hearing test. Moreover, it would have been valuable to include Tower of London task to the current study in order to compare results with previous findings with tone duration. Finally, without differentiation of N1 and MMN, it is most difficult to assess which phenomenon is more prevalent in interpretation of findings. Equal probability control condition (Jacobsen & Schröger, 2001) or similar should be incorporated to make the distinction.

Future directions

Instead of choosing a single electrodes or clustering electrodes according to voltage maps, one could do permutation tests to cluster areas of interest. This would provide systematic and more replicable method. Regardless of the chosen method, several areas should be considered when amplitudes are compared with cognitive variables; far too many researches have chosen only one electrode (e.g. Fz), which rules out the inspection of cognitive functions situated in other domains. In addition, there are various other aspects future studies can address. It would be most informative to use several deviants in the same study, as Kärgel and colleagues (2014) operated. This would rule out the possibility of other variables inflicting the results and could provide more definite answers to the questions related to the differences between, for example, frequency and duration deviants. Moreover, especially since aging is becoming increasingly timely topic, the cognitive processes and its ERP counterparts need more refined understanding. In order to evaluate the very impact of cognitive deficit indicated by a cognitive test, more knowledge is required to understand how it actually affects ERPs and related phenomenon, such as MMN. Furthermore, typically experimental designs involve participants of few age groups, whereas involvement of people from wide range of ages could provide prolific comparison and examination of MMN changes with aging. Lastly, studies could use subsamples of cognitively high-functioning and low-functioning aged participants in order to examine whether cognitive capabilities affect MMN latency or amplitude.

Conclusion

Notwithstanding some limitations, the present study reaffirmed notions on attenuated MMN in aged. In addition, there were important findings on the effect of frequency-deviants on MMN and the relevance to cognitive tests; frequency deviants didn't produce robust correlations between ERP amplitudes and cognitive tests. P2 was attenuated in aged compared to young. Due to the different deviant to other studies concerning MMN, aging and cognitive tests, new directions in research can be formulated. Since fundamental differences concerning aging and neuropsychological changes are being established, practical implications of, for example, success in certain cognitive tests can be thoroughly studied in neuropsychological field. Taking into account the aging of the population, there is a pronounced need for the aforementioned.

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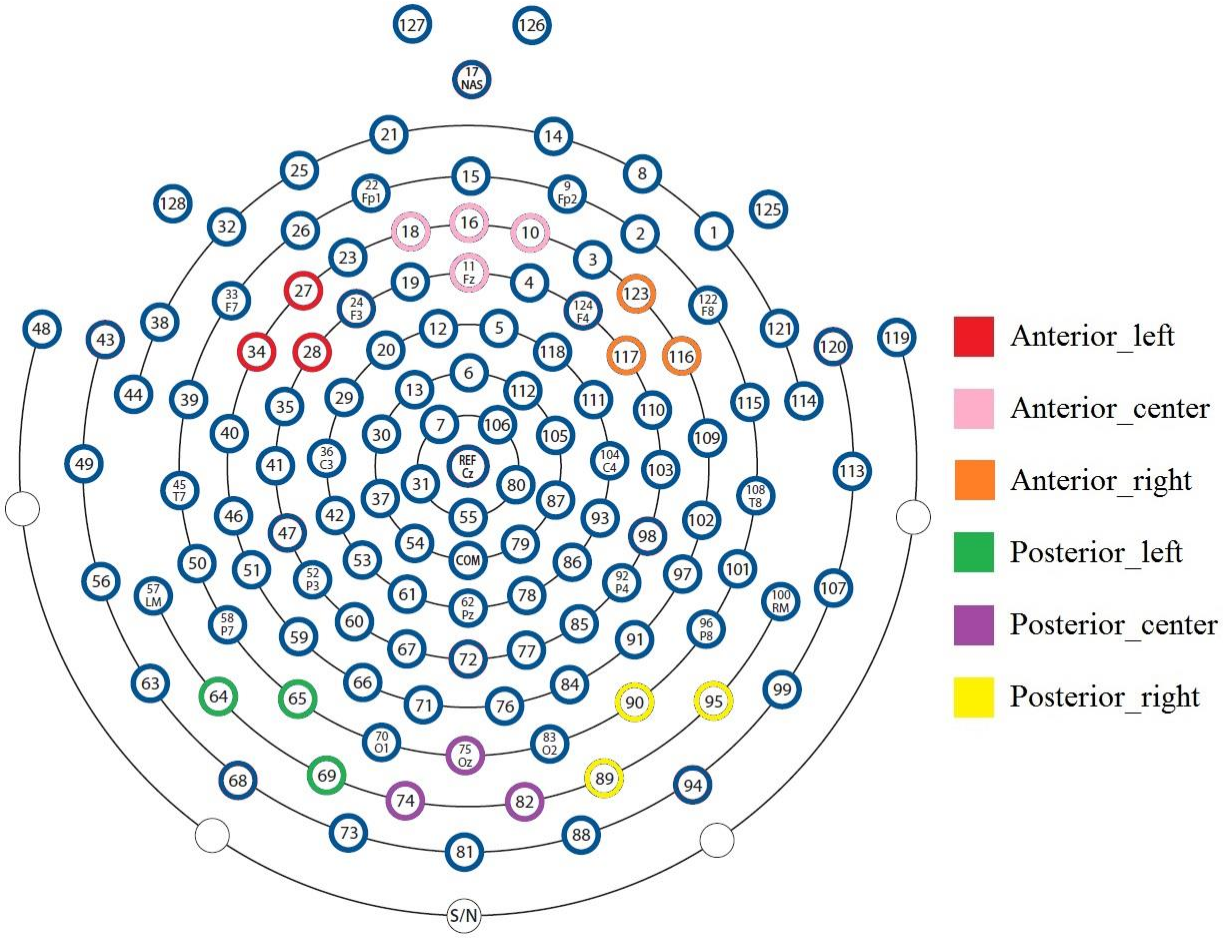
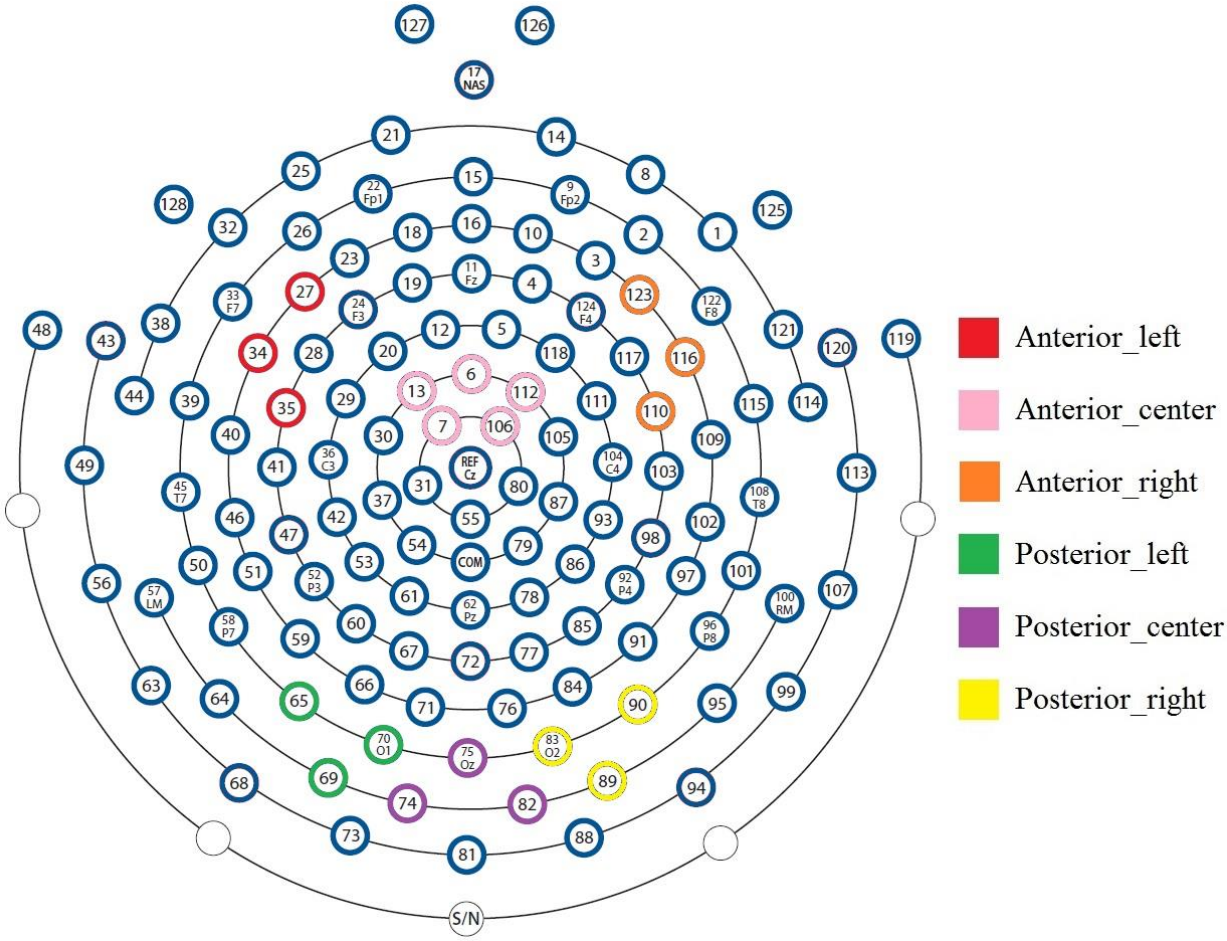
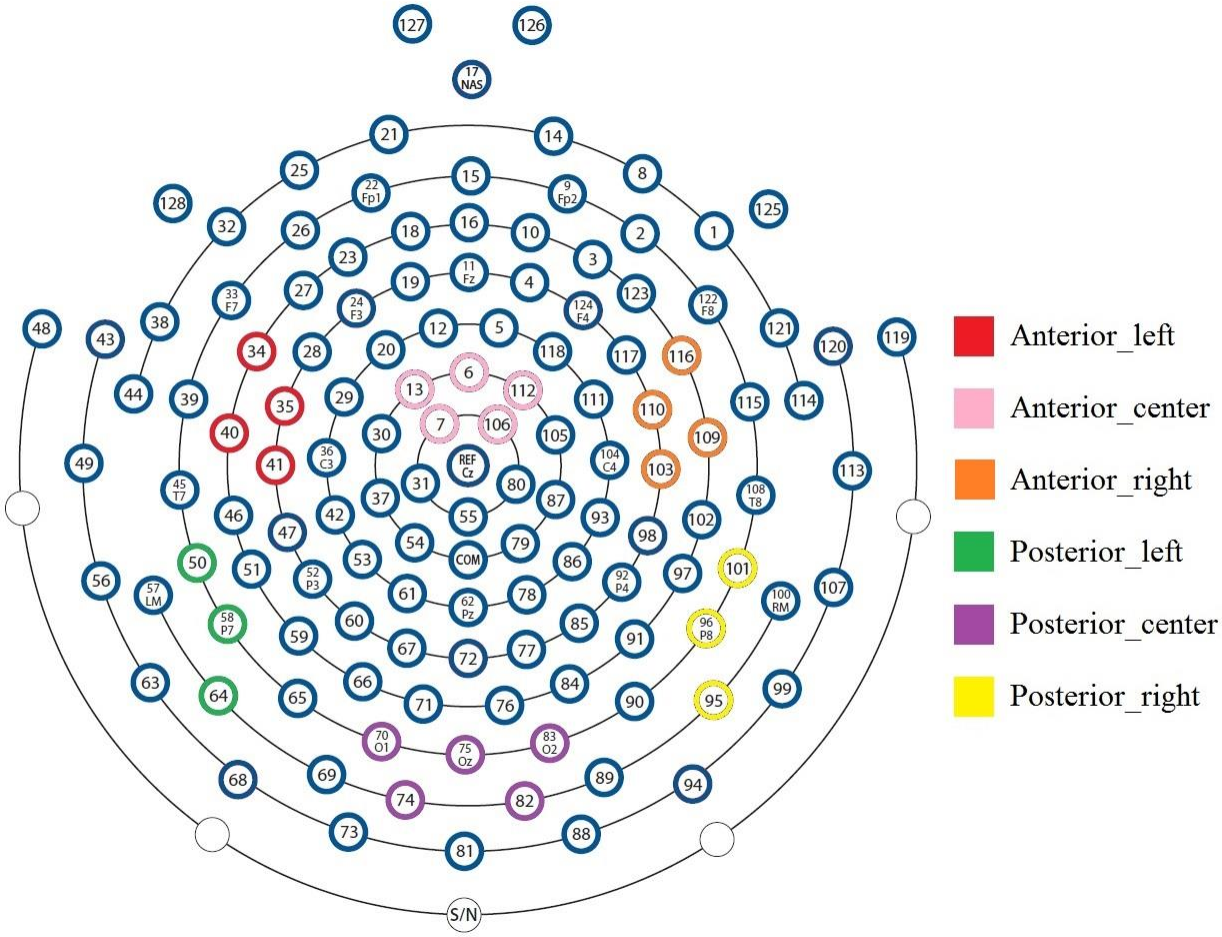
APPENDIX



Appendix 1. *Electrode clustering for the MMN time window (same clustering was applicable for both young and aged).*



Appendix 2. *Electrode clustering for the P2 time window in young.*



Appendix 3. *Electrode clustering for the P2 time window in aged.*

Appendix 4

Table of FDR corrections for Pearson's correlations of cognitive variables versus difference amplitudes in MMN (91-131ms) among aged (controlled for age and hearing)

Rank	Location	P-value	Q-value	Rank	Location	P-value	Q-value
1	Stroop3 errors, anterior right	0.0014	0.0018	58	TMTB, anterior right	0.4783	0.1018
2	Stroop3 errors, posterior left	0.0027	0.0035	59	TMTA, posterior center	0.4821	0.1035
3	Stroop3 errors, anterior center	0.0090	0.0053	60	Logical, anterior right	0.4823	0.1053
4	Stroop3 errors, posterior center	0.0117	0.0070	61	Logical delay, anterior left	0.5046	0.1070
5	Digit-letter, posterior right	0.0240	0.0088	62	Logical, posterior left	0.5394	0.1088
6	Stroop2 errors, posterior left	0.0257	0.0105	63	Span back max, anterior left	0.5556	0.1105
7	Stroop3 errors, anterior left	0.0259	0.0123	64	Tapping right, posterior center	0.5663	0.1123
8	Tapping right, anterior right	0.0304	0.0140	65	Stroop2, posterior left	0.5811	0.1140
9	Tapping right, anterior center	0.0335	0.0158	66	TMTA, posterior left	0.5829	0.1158
10	Stroop2 errors, anterior center	0.0399	0.0175	67	Visual delay, posterior center	0.5878	0.1175
11	Digit-letter max, posterior right	0.0457	0.0193	68	Span back, posterior left	0.5894	0.1193
12	Stroop2 errors, posterior center	0.0477	0.0211	69	Span back, anterior right	0.5981	0.1211
13	TMTA, anterior left	0.0492	0.0228	70	Logical delay, posterior left	0.6147	0.1228
14	Stroop2 errors, anterior left	0.0501	0.0246	71	Visual, anterior center	0.6149	0.1246
15	TMTA, anterior center	0.0515	0.0263	72	Span, posterior center	0.6573	0.1263
16	Stroop2 errors, anterior right	0.0532	0.0281	73	Tapping left, posterior center	0.6595	0.1281
17	Span max, posterior right	0.0543	0.0298	74	Digit-letter, anterior left	0.6616	0.1298
18	Tapping left, anterior right	0.0580	0.0316	75	Stroop3, anterior left	0.6662	0.1316
19	Span max, anterior left	0.0698	0.0333	76	Stroop3, posterior center	0.6938	0.1333
20	Stroop2 errors, posterior right	0.0892	0.0351	77	Digit-letter, posterior center	0.7138	0.1351
21	TMTA, anterior right	0.0928	0.0368	78	Stroop1, anterior right	0.7220	0.1368
22	Stroop1, anterior left	0.0929	0.0386	79	Stroop3, posterior right	0.7422	0.1386
23	Stroop3, posterior left	0.1058	0.0404	80	Visual, anterior right	0.7488	0.1404
24	Stroop3 errors, posterior right	0.1096	0.0421	81	Stroop3, anterior center	0.7512	0.1421
25	Visual delay, posterior left	0.1468	0.0439	82	Span max, anterior right	0.7678	0.1439
26	Visual, anterior left	0.1583	0.0456	83	Digit-letter max, posterior left	0.7734	0.1456
27	Tapping right, anterior left	0.1634	0.0474	84	Logical delay, anterior right	0.7740	0.1474
28	Tapping left, anterior center	0.1677	0.0491	85	Stroop2, posterior right	0.7795	0.1491
29	TMTA, posterior right	0.1716	0.0509	86	Digit-letter, anterior right	0.7871	0.1509
30	Span, anterior left	0.1805	0.0526	87	Stroop1, posterior right	0.8084	0.1526
31	Tapping left, posterior right	0.1939	0.0544	88	Stroop2, anterior left	0.8138	0.1544
32	Stroop3, anterior right	0.1942	0.0561	89	Span back, posterior right	0.8144	0.1561
33	Tapping right, posterior left	0.2074	0.0579	90	Digit-letter max, anterior center	0.8272	0.1579
34	Tapping left, posterior left	0.2231	0.0596	91	Span, anterior center	0.8312	0.1596
35	Logical, anterior center	0.2314	0.0614	92	Visual delay, posterior right	0.8466	0.1614
36	Visual delay, anterior left	0.2393	0.0632	93	Span, anterior right	0.8483	0.1632
37	Stroop1, anterior center	0.2457	0.0649	94	Digit-letter, posterior left	0.8539	0.1649
38	Tapping right, posterior right	0.2480	0.0667	95	Digit-letter max, anterior right	0.8605	0.1667
39	TMTB, posterior center	0.2890	0.0684	96	Span back max, posterior center	0.8702	0.1684
40	Tapping left, anterior left	0.3162	0.0702	97	Logical, posterior right	0.8868	0.1702
41	TMTB, anterior center	0.3394	0.0719	98	Span back, posterior center	0.9047	0.1719
42	TMTB, anterior left	0.3446	0.0737	99	Digit-letter max, anterior left	0.9053	0.1737
43	Visual delay, anterior center	0.3638	0.0754	100	Span, posterior left	0.9096	0.1754
44	Visual delay, anterior right	0.3878	0.0772	101	Span back max, posterior right	0.9128	0.1772
45	TMTB, posterior left	0.3882	0.0789	102	Logical delay, posterior center	0.9276	0.1789
46	Logical, anterior left	0.3919	0.0807	103	Stroop2, posterior center	0.9435	0.1807
47	Span back max, anterior right	0.4032	0.0825	104	Stroop2, anterior right	0.9589	0.1825
48	Logical delay, posterior right	0.4050	0.0842	105	Visual, posterior left	0.9611	0.1842
49	Span, posterior right	0.4085	0.0860	106	Logical, posterior center	0.9632	0.1860
50	Stroop1, posterior center	0.4117	0.0877	107	Span back, anterior center	0.9651	0.1877
51	Logical delay, anterior center	0.4136	0.0895	108	Span max, posterior center	0.9667	0.1895
52	Span back, anterior left	0.4146	0.0912	109	Visual, posterior center	0.9715	0.1912
53	Visual, posterior right	0.4201	0.0930	110	Stroop1, posterior left	0.9832	0.1930
54	Digit-letter max, posterior center	0.4534	0.0947	111	Span back max, anterior center	0.9842	0.1947
55	Span max, anterior center	0.4624	0.0965	112	Stroop2, anterior center	0.9846	0.1965
56	TMTB, posterior right	0.4634	0.0982	113	Span max, posterior left	0.9981	0.1982
57	Digit-letter, anterior center	0.4726	0.1000	114	Span back max, posterior left	0.9985	0.2000

All the p-values are ranked by the smallest value. The p-value is compared to the q-value (= rank divided by total number of p-values times FDR value). If the p-value is smaller than the corresponding q-value, the finding is significant at the FDR value in question. In the current study, the FDR value was set at 0.2. Significant findings are highlighted.