A CROSS-SECTIONAL STUDY OF NORMAL AGING ASSOCIATED WORKING MEMORY DIFFERENCES

by

YUAN GAO

(Under the Direction of Brett A. Clementz)

ABSTRACT

The current study used a cross-sectional design, comparing younger, middle-aged, and older adults' cortical neural activation recorded by dense-array electroencephalography (EEG) in an auditory working memory task. The operational span task (OSPAN) was administered to all subjects to evaluate their working memory capacity. Response latency and strength of the evoked EEG potentials associated with sensory stimuli processes (N100, P200, N200) and working memory (P300) were compared across age groups. Our findings indicate that middle-aged and old subjects had altered cortical neural activations (N100, P200, and N200) during sensory processes compared to young subjects, suggesting an age-associated overexcitement. This reduced inhibitory regulation from sensory processes resulted in sequential changes in P300, which corresponded with subjects' behavioral performance quality in OSPAN test, i.e. old subjects had the lowest OSPAN scores and the young group had the highest OSPAN scores. The findings suggest that although age-associated cortical neural activation alternations are highly likely to associate with or lead to older subjects' poorer behavioral performance tests; these cortical and behavioral changes can start during individual's middle age.

INDEX WORDS: Aging, EEG, Working Memory, OSPAN

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YUAN GAO

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by

YUAN GAO

Major Professor:	Brett A. Clementz
Committee:	Jennifer E. McDowell L. Stephen Miller Leonard W. Poon Nash Unsworth

Electronic Version Approved:

Maureen Grasso
Dean of the Graduate School
The University of Georgia
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DEDICATION

The dissertation is inspired by Drs. Robert Bretscher and Anne Bretscher's proactive attitude of life and their dedicated effort to fight against Pick's disease.

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Chapter 1 Introduction

Age Differences of Working Memory

Working memory is a set of complex cognitive processes, including attentional information maintenance and volitional information manipulation. The former enables online holding of verbal, auditory, and visuospatial information for sensory memory and long-term memory storage; the latter is associated with central executive functions (Reuter-Lorenz & Sylvester, 2005). Brain regions associated with working memory include the frontal cortex, parietal cortex, anterior cingulate, and parts of the basal ganglia. Working memory tasks requiring online information maintenance activate the prefrontal cortex and posterior parietal cortex (Ruge & Braver, 2006); tasks requiring executive functions activate the dorsolateral prefrontal cortex (Mesulam, 2000).

Normal aging starts to influence working memory during young adulthood. The influences gradually intensify among adults over 50 years of age (Deater-Deckard & Mayr, 2005; Schaie & Zanjani, 2006; Verhaeghen & Salthouse, 1997; Wills & Schaie, 2005, 2006). Older adults have a smaller working memory span than younger adults (Unsworth, Heitz, Schrock, & Engle, 2005); they are less able to inhibit task-irrelevant information effectively, leading to a "mental clutter" that diminishes their working memory capacity (Maylor, Schlaghecken, & Watson, 2005). Reduced working memory capacity compromises older adults' ability to manipulate the same amount of information; therefore, they need more time to achieve the same level of behavioral performance as younger adults (Park et al., 2003; Verhaeghen, Cerella, Bopp, & Basak, 2005; Verhaeghen & Salthouse, 1997). When behavioral performance speed is not required and older adults are given enough time to finish the tasks, they can perform with the same accuracy level

as younger adults. In contrast, when time is limited, older adults often sacrifice performance accuracy to speed (Reuter-Lorenz & Sylvester, 2005).

Aging of the human brain can affect older adults' working memory ability. A large number of cerebral cortical regions undergo a series of structural changes during normal aging, i.e. decreased synaptic density, reduced number of neurons, decreased neuron size, decreased callosal volume, and reduced white matter volume (Sowell et al., 2003). These changes can lead to, or at least increase the likelihood of functional differences (investigated by cross-sectional studies) and changes (investigated by longitudinal studies), which can be captured by neuropsychological assessments (Coffey et al., 2001) and cerebral cortical activities observed in neuroimaging studies. For instance, prefrontal cortex (PFC), the neural architecture closely associated with working memory, is one of the most vulnerable cerebral cortical regions affected by normal aging (Rajah & D'Esposito, 2005).

Older adults' altered behavioral response speed and response accuracy in working memory tasks often coincides with different cortical activations when compared with gender and education-matched younger participants (Logan, Sanders, Snyder, Morris, & Buckner, 2002). Although older adults tend to display slower performance and lower accuracy in working memory tasks than younger adults (Reuter-Lorenz & Sylvester, 2005), some do have similar behavioral performance as younger adults when response speed is not required. These older adults are referred to as the "high performance group." The high performers have additional neural activities in the right dorsal lateral PFC in working memory tasks (Reuter-Lorenz & Sylvester, 2005), which is known as the "Hemisphere Asymmetry Reduction in Older Adults" (HAROLD) model. HAROLD conceptualizes the fact that older high performers are more likely to show bilateral PFC activates in working memory tasks (Cabeza et al., 1997; Cabeze, Anderson,

Locantore, & McIntosh, 2002; Rosen et al., 2002). The extra neural activities suggest that older high performers engage more brain regions than younger adults to successfully meet the task requirements (Reuter-Lorenz & Lustig, 2005). This HAROLD pattern can be attributed to either an age-associated neural network compensatory recruitment, which is temporarily task-context dependent, or an age-associated cortical neural re-organization, during which hemispheric lateralization is gradually diminishing (Raz et al., 2005).

Electrophysiological Study of Working Memory Aging through P300

One critical aspect in studying aging-associated differences in working memory is to track the temporally evolving patterns of cerebral cortical activations, which cannot be directly assessed using either neuropsychological or fMRI based-neuroimaging studies. The scalp recorded dense-array electroencephalograph (EEG) can measure cerebral cortical activations on a millisecond temporal scale, therefore, EEG is an ideal tool to investigate the temporal dynamics of working memory differences during normal aging. Subcortical and cortical neuronal activities generate EEG; those signals are the summation of neural postsynaptic potentials, with fluctuating voltage values as a function of time. EEG amplitude indexes the strength of the scalp-recorded electrical signals. Those temporal fluctuations can be averaged under the same experiment conditions, known as event-related potentials (ERPs).

P300 is an ERP with peak latency in the range of 300 to 800 ms after the onset of an attended sensory stimulus. P300 indexes working memory functions across sensory modalities (Groom et al., 2008; Tekok-Kilic, Shucard, & Shucard, 2001). The oddball paradigm is often used to generate P300, in which the target (or oddball) stimuli are embedded in a train of nontarget (or standard) stimuli. The target possesses unfamiliar sensory information as opposed to the standard. Subjects are required to either actively respond to each target by pressing buttons

or passively attend to each target by silently counting the number of such events. Both task requirements will generate a response with subjects' attention being automatically shifted towards the target (Ranganath & Rainer, 2003).

Theoretically, P300 is considered an index working memory updating and attention relocation, which reflects neural activations in response to "new" or "unexpected" stimulations (Kramer & Hillman, 2006). P300 amplitude is associated with attention resource allocation during working memory updating; larger P300 amplitudes indicate more attention resources. P300 latency correlates negatively with mental functions; shorter latency indicates superior cognitive performance (Soltani & Knight, 2000).

Yung healthy subjects' P300 has a scalp topographical distribution with maximum amplitude over central-parietal midline recording sensors. The neural networks generating P300 include, but are not limit to, locus coeruleus (LC, Soltani & Knight, 2000), temporal parietal junction, supramarginal gyrus, medial temporal lobe, and the caudal parts of the superior temporal cortex (Halgren et al., 1980; McCarthy, Wood, Williamson, & Spencer, 1989; Ranganath & Rainer, 2003; Soltani & Knight, 2000). Auditory P300, in particular, is generated in temporal-parietal junction and PFC (Knight, Scabini, Woods, & Clayworth, 1989; Polich, 2007; Menon, Ford, Lim, Glover, & Pfefferbaum, 1997; Soltani & Knight, 2000).

P300 is sensitive to age. Older adults have smaller P300 amplitude and longer P300 latency than younger adults (Anderer, Pascual-Marqui, Semlitsch, & Saletu, 1998; Anderer, Semlitsch, & Saletu, 1996; Chao & Knight, 1996; Friedman, Kazmersik, & Fabiani, 1997; Kok, 2000; Polich, 1996; 1997). P300 scalp topography also differs between older and younger adults. Older adults tend to have a frontally distributed P300; younger adults have a parietal distribution (Friedman et al., 1997) although the extent and characteristics of these distributional differences have yet to be

detailed. The age differences of P300 topography indicate either the compensatory activations of frontal neural generators in response to the deficient parietal neural generators or a result of age-associated cerebral cortical neural re-organization among older adults (Anderer et al., 1998; Downs, Hymel, & Cranford, 2001; Fabiani, Friedman, & Cheng, 1998; Friedman, Cycowicz, & Dziobek, 2003; Friedman et al., 1997; Frodl et al., 2000).

Operational Span Task

The operational span task (OSPAN) is a psychometric assessment of working memory capacity (Turner & Engle, 1989). OSPAN measures working memory operations that require executive control processes; it provides an efficient and reliable behavioral assessment of age-associated working memory differences (Turner & Engle, 1989). OSPAN involves dual processes, i.e. a math calculation and a word memorization. A sequence of task items is presented in every trial; each trial consists of a math equation and an unrelated word. First, subjects are required to determine whether the math equation is correct. Second, they are asked to memorize the words. After all equations and words in on trial are presented, subjects are asked to recall the words in the same order as they were presented. A successful completion of one trial is to have both correct judgments of the math equations across trials and to correctly recall in proper order the memorized words.

OSPAN task prevents memory strategies such as grouping and rehearsal (Turner & Engle, 1989). Subjects with higher OSPAN scores also have better behavioral performance in other cognitive tasks requiring attention control, especially those under distraction and interference conditions (Kondo et al., 2004; Unsworth et al., 2005). Older adults typically have lower accuracy and longer reaction time than younger adults in OSPAN tasks. Age differences in OSPAN task performance also correlate with PFC activities, i.e. younger poor performers and

older subjects activate additional PFC regions in the left hemisphere compared to younger good performers (Smith, et al., 2001). ERPs also correlate with OSPAN performance. Subjects with higher OSPAN scores tend to have larger P300 amplitudes than lower OSPAN participants (Nittono, Nageishi, Nakajima, & Ullsperger, 1999). Combining ERP and OSPAN measures can provide a comprehensive investigation of age-associated working memory differences (Lefebvre, Marchand, Eskes, & Connolly, 2005).

Compromised Sensory Processes and Working Memory Deficits

Normally aged older adults have compromised working memory ability. Questions remain regarding whether this deficit starts at a higher level of cortical processing. Any working memory task will start with initial sensory stimuli registration, progress to task-relevant contextual information evaluation and updating, and end with behavioral responses. Sensory registration and context updating are two essential processes. Normal aging can alter the outcome of sensory processing. For example, aged animals have decreased GABAergic inhibitory regulation in primary auditory cortex, which is associated with a loss of response selectivity in neural circuitries utilizing GABA in primary sensory cortices (Ling, Hughes, & Caspary, 2005). The altered outcomes of sensory processing are highly likely to result in sequential cortical neural activation and/or behavioral response differences in working memory processes. Therefore, it is necessary to investigate sensory processes in order to determine the starting point of the altered cortical neural activations associated with normal aging.

Auditory N100 and P200 index early sensory processes. N100 occurs around 100 ms after stimuli onset, followed by P200 (ERP occurring around 200 ms). N100 is sensitive to stimulus characteristics and attentional manipulations (Clementz, Barber, & Dzau, 2002; Huotilainen et al., 1998; Näätänen & Picton, 1987; Teder, Alho, Reinikainen, & Näätänen, 1993; Woldorff et al.,

1993). N100 depends on the anatomical structure of the auditory pathway (Näätänen & Picton, 1987; Näätänen, Teder, Alho, & Lavikainen, 1992; Pantev, Hoke, Lutkenhoner, Lehnertz, & Spittka, 1986). The primary determinants of N100 are neurons in and near auditory cortex (e.g., Chao, Nielsen-Bohlman, & Knight, 1995; Grunwald et al., 2003). N100 has a main source posterior to primary auditory cortex in planum temporale (Godey, Schwartz, de Graaf, Chauvel, & Liegeois-Chauvel, 2001; Lutkenhoner & Steinstrater, 1998). Studies on age-associated differences of N100 have mixed results. Older adults are reported to have N100 with larger (Anderer et al., 1996; Chao & Knight, 1997; Ford & Pfefferbaum, 1991; Gao, Boyd, Poon, & Clementz, 2007; Polich, 1997), smaller (Hymel, Cranford, & Stuart, 1998), or similar amplitude as younger adults (Amenedo & Diaz, 1998; Bennett, Golob, & Starr, 2004; Iragui, Kutas, Mitchiner, & Hillyard, 1993; Laffont et al., 1989).

P200 is also sensitive to physical parameters of sensory stimuli and is modulated by attention (Golob & Starr, 2000). Studies addressing age differences of auditory P200 have inconsistent results. Older adults are reported to have larger (Amenedo & Diaz, 1999; Bennett et al., 2004; Chao & Knight, 1996) or smaller (Bertoli, Smurzynski, & Probst, 2002) auditory P200 than younger adults. Age differences of P200/N200 latency are also inconsistent across studies. Age associated latency increase (Homberg et al., 1986; Iragui et al., 1993) and no significant latency changes (Anderer et al., 1996; Barrett, Neshige, & Shibasaki, 1987; Pfefferbaum, Ford, Wenegrat, Roth, & Kopell, 1984) have both been observed among older adults.

The Current Study

The current experiment was developed based upon a synthesis of previous studies investigating normal aging associated differences in working memory. First, behavioral working memory performance measures in previous studies did not have the power to differentiate

individual participants with different levels of working memory ability due to the simplicity of the tasks. It is possible that the observed difference associated with aging can also be accounted for by working memory ability variations rather than aging alone. Second, neuropsychological assessments and fMRI-based studies do not emphasize the temporal dynamics of cortical activations in working memory tasks, which leaves out the opportunity to investigate the starting point of normal aging associated differences at the cortical level.

The current study used a cross-sectional design, comparing healthy young, middle-aged, and old subjects' behavioral performance in an OSPAN task and their cortical ERPs recorded in an auditory oddball paradigm. A total of 51 (17 young, 18 middle-aged, and 16 older) subjects' data were analyzed. We found that middle-aged and old subjects had larger cortical neural activations (N100 and P200) during sensory processes compared to young subjects, which is attributed to age-associated reduction of cortical inhibitory modulation. They had smaller activations (N200 and P300) during working memory processes, which is attributed to either inefficient sensory evaluation induced contextual updating compromise or an altered subcortical and cortical neural circuitries generating P300. Age differences of P300 corresponded with behavioral performance in OSPAN test, i.e. old subjects had the lowest OSPAN scores and the young group had the highest OSPAN scores. The findings suggest that age-associated cortical neural activation alternations are highly likely to associate with or lead to older subjects' poorer behavioral performance tests; these cortical and behavioral differences can start as early as in one's middle age.

Chapter 2 Methods

Subject Recruitment

The study was approved by the Institutional Review Board at the University of Georgia. Young subjects were recruited from the human subject research pool at the University of Georgia. Middle-aged and old subjects were recruited through fliers posted in Athens community.

Individuals, who contacted the researchers, were first given a standardized clinical telephone interview to exclude persons with signs of Alzheimer's disease, mild cognitive impairment, or other neurological conditions that can affect brain functioning, or any major psychiatric disorders. The selected subjects from the telephone interview were given the Mini-Mental State Exam (MMSE) (Folstein, Folstein, & McHugh, 1975). Individuals, who scored between 24 and 30, proceeded to the information subscale of WAIS-III (Wechsler, 1997) to assess the global cognitive functions among age groups. Binaural hearing threshold was determined for all individuals by the method of limits (in 5 dB steps; Davis & Haggard, 1982) with 0.5 KHz, 1 KHz, 2 KHz, and 4 KHz pure tones generated by an auditory stimulator (Grass Model 10H2S audiometric headphones and Grass Model S10CTCM auditory stimulator). Individuals with hearing threshold within normal range were asked to participate (middle-aged and old individuals' hearing thresholds were age-adjusted when compared with young individuals).

A total of 17 young (18-25 years of age, 18.0 +/- 0.3), 18 middle-aged (45-55 years of age, 49.4 +/- 0.94), and 16 old (65-75 years of age, 68.4 +/- 1.17) right-handed individuals were recruited. All subjects were given a brief oral description of the experiment procedures prior to testing. All subjects were asked to provide written informed consents prior to experiment.

Materials and Tasks

Subjects were instructed to refrain from smoking and caffeine ingestion for at least 60 minutes before testing.

OSPAN test. All selected subjects were given the OSPAN (see Appendix; Turner & Engle, 1989) to measure working memory capacity. Subjects were asked to solve a math operation by deciding whether an equation was correct or wrong (e.g. "2*4+1=10"). After solving the operation, subjects were presented with an unrelated word (e.g. "tree") for one second and they were required to memorize the word for a later memory test. After all equations and words were presented, subjects were asked to write down the words in the same order as they were presented (Unsworth et al., 2005). Subjects would gain points only when they made the correct judgments of the math equations, accurately recalled all the words, and wrote the words in the correct order. All subjects received three practice trials prior to testing. A total of 42 OSPAN trials were used.

Oddball paradigm. Auditory stimuli were created using NCH tone generator software (Version 2.0; NCH Swift Sound, Bruce, Australia). Tones were programmed into Presentation V9.0 (Version 9.0, Neurobehavioral Systems, Inc., Albany, CA); they were delivered binaurally through Etymotic insert earphones (Etymotic Research, Elk Grove Village, IL) at 76 dB SPL.

An auditory oddball paradigm with a total of 864 trials (720 trials with 1 kHz standards, 144 trials with 1.2 kHz targets, 100ms duration tones with 5ms rise and fall, 1 sec ISI) was used. Tones were quasi-randomly presented, such that one to nine standard tones occurred between target tones. The 864 trails were divided into four blocks: 216 trials in each block with 36 target stimuli and 180 standard stimuli. Target stimuli never occurred on consecutive trials. A dim white cross, on which all subjects were asked to fixate throughout EEG recording, was presented in the center of a computer screen 100 cm away from the nasion. Subjects were asked to silently count

the number of the target stimuli in each block. The experimenter asked the subjects to report their target counting during testing breaks. Subjects' target counting was recorded. Prior to data recording, sample stimuli were given to all subjects to ensure they understood the task.

EEG data collecting. EEG data were recorded vertex-referenced using a 256 channel Geodesic Sensor Net and two linked 128 channel NetAmps 200 amplifiers (Electrical Geodesics; EGI, Eugene, OR). Electrode impedances were kept below 50 kV (the EGI manufacturer recommended value when using high input impedance amplifiers). Data were sampled at 500 Hz with an analog filter bandpass of 0.1–250 Hz during data collection and re-sampled offline to 250Hz for analyses. EEG sensors covering subjects' neck and cheeks were eliminated, leaving 210 recording sensors for further analyses.

EEG Data Preprocessing

Artifacts removal. Signals in the EEG recordings associated with eye-blink, cardiac activities, and muscle artifacts were eliminated from the ongoing EEG data using independent component analysis (ICA). ICA can identify artifacts in EEG data by linear decomposition without distorting the signal of interest (see, EEGLAB; Delorme & Makeig, 2004). Artifacts in the EEG data were extracted as independent components. Artifact-free EEG data were obtained, therefore, by eliminating the artifactual sources. This procedure was performed in EEGLAB (version 6.01b) and Matlab (version 7.6.0).

Prescreening and ERP segmentation. Artifact-free EEG data were digitally filtered from 0.5-100 Hz (12 dB down at each edge) with a zero-phase-shift 3rd order Butterworth filter, and notch-filtered at 60 Hz (+/-2 Hz stop bands). The filtered data were segmented around stimulus triggers in BESA 5.0 (Berg & Scherg, 1994; Ille, Berg, & Scherg, 2002) into two types of averaged responses for each subject, i.e. standard auditory stimuli-evoked ERPs and target

stimuli-evoked ERPs. The preprocessed EEG data were exported from BESA into a Matlab readable format for further analyses.

ERP Components Latency and Strength Quantification

Global field power calculation. Global field power (GFP) is a reference-free measure of the local activations within a measured electrical field. It is used to identify the timing of cortical activations of interest (Lehmann & Skrandies, 1984). GFP takes account of signals from all recording sensors. It is a concise and efficient measurement of the overall ERP signal strength, which is defined as

$$\mathrm{GFP}(t_k) \equiv \sqrt{\frac{\sum_{i=1}^{n}\sum_{j=1}^{n}[u_i(t_k) - u_j(t_k)]}{2n}} \qquad (1)$$

where $u_i(t_k)$ and $u_j(t_k)$ are the recorded ERPs at each EEG recording sensor at the time t_k taken in all possible pairs, measured relative to a common reference, and n is the number of recording sensors used (n is equal to 210 in current study). The difference between u_i and u_j at time t_k is independent of the reference sensor used. GFP measures the spatial variation of ERPs at each time point over a large array of EEG sensors. GFP, as described in Eq. (1), represents a spatial standard deviation and it is often used as a standard approach to determine ERP latency in multi-channel EEG recordings.

Data were imported into Matlab. GFP of each subject was calculated as in Eq. (1). A 2nd order Butterworth filter (0.5-20 Hz) was applied to individuals' GFP to eliminate noise signals. N100 and P200 ERP components were identified from the standard stimuli evoked responses among young, middle-aged, and old subjects. N100, N200, and P300 were identified from the

target stimuli evoked responses among young, middle-aged, and old subjects. An additional P200 was also identified from the target stimuli evoked responses among old subjects (see Figure 1).

ERP latency The latencies of standard and target stimuli-evoked auditory responses of each individual subject were determined from their GFP, where the latency of the peak amplitude within a time window was denoted as the latency for that particular ERP. For example, N100 is known to have the peak amplitude between 80 ms and 120 ms after the onset of auditory stimuli (Gilmore, Clementz, & Buckley, 2004; Gilmore, Clementz, & Buckley, 2005; Irimajiri, Golob, & Starr, 2008). N100 latency for each individual subject was determined as the time point when the GFP reached its maximum value within the 80 ms to 120 ms time window. The same approach was used to quantify the peak latency for P200, N200, and P300.

ERP strength. Strength of ERPs was quantified by averaging the voltage values at the peak latency of a particular component plus one EEG data sample backward and one EEG data sample forward in time from the 210 sensors.

Age Effect Analyses

Latency differences. N100 latencies were compared by a three by two mixed ANOVA test, with age (young versus middle-aged versus old) as the between subjects factor and auditory stimuli types (standards versus target) as the within subjects factor. P200, N200, and P300 latency were compared by a one-way ANOVA with age as the between subjects factors. Old subjects' P200 latencies were subjected to a paired t-test to compare stimuli type (standard versus target) differences. ANOVA and t-test tests were programmed in Matlab (version 7.6.0 with the statistical tool box installed).

Strength differences. To assess the strength differences of the ERPs, a three by two mixed ANOVA analyses, with age as the between subjects factor and auditory stimuli types as the

within subjects factor, was performed on each of the 210 recording sensors for N100; a one factor ANOVA with age as the between subjects factor was performed on each of the 210 recording sensors for P200, N200, and P300. Paired t-tests were performed to assess stimuli type effects (standard versus target) of old subjects' P200 on each of the 210 sensors. To control family-wise error rates, the method of clustering was used (Forman et al., 1995) to take account of the non-independence of data from adjacent electrodes. Significance levels (Krusemark, Campbell, & Clementz, 2008) were determined based on the noise level of the data estimated from the prestimulus baseline and Monte Carlo simulations calculated using AlphaSim (Cox, 1996). To maintain the familywise alpha lower than .01, ANOVA test for any individual sensor required at least six surrounding sensors (the distances between each sensor should be equal to or less than 4 mm) with effects statistically significant at $p<.035$.

ERP topography correlations. Correlation coefficients (r) of ERP strength from each individual subject with the average ERP strength of the three age groups were calculated to quantify the spatial distributions similarity of ERP scalp topography distribution. Correlations of each subject's ERP strength with the same age group's average ERP strength (for example, r values of each young subject's N100 strength with young subjects' group average N100 strength) were used to quantify the representativeness of average ERP spatial topography distribution.

The within-age group r values of N100 were subjected to a three by two mixed ANOVA analyses, with age as the between subjects factor and auditory stimuli types as the within subjects factor. The within-age group r values of P200 (evoked by standard stimuli for the three age groups), N200, and P300 were subjected to one-way ANOVA analyses, with age as the between subjects factor. For old subjects' P200 components, r values were subjected to a paired t-test to assess stimuli type effects.

OSPAN differences. All subjects' OSPAN scores were ranked with an ascending order regardless of the age groups. The raw scores were transferred into rank orders for each subject. A one-way Friedman Nonparametric ANOVA with age as between subjects factor was used to compare age differences of OSPAN scores.

OSPAN Rank Effect Analyses

OSPAN score rank. Regardless of age groups, the 51 subjects were divided into low OSPAN group (13 subjects: 7.69 +/- 0.67), whose raw scores were equal to or below 10; median OSPAN group (26 subjects: 16.96 +/- 0.58), whose raw scores were between 11 and 21 (including 11 and 21); high OSPAN group (12 subjects: 28.50 +/- 1.77), whose raw scores were equal to or above 22 (Unsworth, Schrock, & Engle, 2004).

Latency differences. N100 latencies were compared by a three by two mixed ANOVA analyses, with OSPAN rank (low versus median versus high) as the between subjects factor and auditory stimuli types as the within subjects factor. P200, N200, and P300 latency were compared by a one-way ANOVA with OSPAN rank as the between subjects factor.

Strength differences. N100 evoked by standard and target stimuli, P200 evoked by standard stimuli, N200 and P300 evoked by target stimuli were identified for low, median, and high OSPAN groups. To assess the strength differences of the ERPs, a three by two mixed ANOVA analyses, with OSPAN rank as the between subjects factor and auditory stimuli types as the within subjects factor, was performed on each of the 210 recording sensors for N100; a one-way ANOVA with OSPAN rank as the between subjects factor was performed on each of the 210 recording sensors for P200, N200, and P300. The same methods of clustering were used to control family-wise error rates.

ERP topography correlations. Correlation coefficients (r) of ERP strength from each individual subject with the average ERP strength of the three OSPAN rank groups were calculated to quantify the spatial distributions similarity of ERP scalp topography distribution. Correlations of each subject's ERP strength with the same OSPAN rank group's average ERP strength (for example, r values of each low OSPAN subject's N100 strength with low OSPAN subjects' group average N100 strength) were used to quantify the representativeness of average ERP spatial topography distribution.

The within-OSPAN group r values of N100 were subjected to a three by two mixed ANOVA analyses, with OSPAN rank as the between subjects factor and auditory stimuli types as the within subjects factor. The within-OSPAN group r values of P200, N200, and P300 were subjected to one-way ANOVA analyses, with OSPAN rank as the between subjects factor.

Chapter 3 Results

Subjects Selection Criteria

All selected subjects had MMSE score above 24 (young=29.78 +/- 0.23; middle-aged=29.29 +/- 0.38; old=28.86 +/- 0.45); the raw scores from WAIS-III information subscale were comparable among age groups (young=21.67 +/- 0.71; middle-aged=23.67 +/- 0.80; old=23.20 +/- 0.74). Subjects' age-adjusted hearing thresholds were all within the normal range (young=10.97 +/- 1.05 dB; middle-aged=13.39 +/- 1.33 dB; old=12.13 +/- 1.51 dB, see NIOSH, 1998).

Age Effects

No age differences were found on target stimuli counting ($F_{2,48}$=0.79, p=.46); all age groups had high accuracy rates (young: 99.7% +/- 0.2%; middle-aged: 98.5% +/- .09%; old: 97.2% +/- 2.1%).

N100. N100 was evoked by both standard and target stimuli. ANOVA analyses did not reveal age differences of N100 latency ($F_{2,96}$=2.76, p=.07). N100 evoked by standard stimuli (99.22 +/- 1.24 ms) had a shorter latency than N100 evoked by target stimuli (103.07 +/- 1.45 ms), $F_{1,96}$=4.84, p=.03. No interaction between age and stimuli type was found ($F_{2,96}$=0.80, p=.45), see Figure 1. Age differences of N100 amplitude were found from one parietal sensor cluster, where young subjects had the weakest average amplitude, middle-aged subjects had the intermediate average amplitude, and old subjects had the strongest average amplitude (see Figure 2). Stimuli type effects were also found from one frontal sensor cluster, with standard stimuli having weaker average amplitudes than target stimuli (see Figure 2). No age differences ($F_{2,96}$=2.18, p=.12) or stimuli type effects ($F_{1,96}$=0.40, p=.53) were found on N100 topography correlation coefficients, indicating that the three age groups did not differ on within-group

similarity of N100 scalp topography distribution (see Figure 4); indeed, the spatial distributions of N100 were remarkably similar across the age groups.

P200. Significant age differences were found for P200 latency, $F_{2,48}$=4.94, p=.01. Young subjects (171.27+/- 8.21 ms) had shorter P200 latency than middle-aged (186.15 +/- 7.97 ms) and old subjects (194.25 +/- 8.46 ms). No differences existed between middle-age and old subjects. Old subjects had longer latency for standard stimuli evoked P200 than target stimuli evoked P200 (175.06 +/- 2.65 ms), t_{15}=2.13, p=.05, see Figure 1. Age differences of P200 amplitude were found from one frontal sensor cluster and one parietal/occipital sensor cluster, with young subjects having the weakest average amplitude, middle-aged subjects having the intermediate average amplitude, and old subjects having the strongest average amplitude (see Figure 3). No stimuli type effects were found between old subjects' P200.

Age differences of P200 topography correlation coefficients were found, $F_{2,48}$=16.75, p=<.001, with young subjects (R=.68 +/- .03) having a smaller within-group topographic similarity than middle-aged (R=.84 +/- .02) and old subjects (R=.88 +/- .03); no differences were found between middle-aged subjects and old subjects (see Figure 4). The differences between young and older subjects indicate that the young subjects had greater individual variability of P200 scalp topographical spatial distributions than older subjects. Significant stimuli type effects of old subjects' P200 topography correlation coefficients were found, t_{15}=5.88, p=<.001. Old subjects had larger topographic correlation for standard stimuli evoked P200 (R=.88 +/- .02) than target stimuli evoked P200 (R=.78 +/- .03), see Figure 4. This difference suggests that old subjects' standard stimuli evoked P200 had smaller topography individual variability than target stimuli evoked P200.

N200. Significant age differences were found for N200 latency, $F_{2,48}$=7.23, p=.002. Young (208.00 +/- 5.01 ms) and middle-aged (211.00 +/- 4.87 ms) subjects had shorter N200 latencies than old subjects (230.50 +/- 5.16 ms). No difference existed between young and middle-aged subjects (see Figure 1). Age differences of N200 amplitude were found from one frontal/central sensor cluster and one parietal/occipital sensor cluster, with young subjects having the strongest average amplitude, middle-aged subjects having the intermediate average amplitude, and old subjects having the weakest average amplitude (see Figure 3). No age differences ($F_{2,96}$=1.23, p=.30) were found on N200 topography correlation coefficients, indicating that the three age groups did not differ on the within-groups similarity of N200 spatial topography distribution.

P300. Significant age differences were found for P300 latency, $F_{2,48}$=35.11, p<.001. Young (321.41 +/- 11.12 ms) and middle-aged subjects (329.22 +/- 10.80 ms) had shorter P300 latencies than old subjects (381.75 +/- 11.46 ms). No differences existed between young and middle-aged subjects (see Figure 1). Age differences of P300 amplitude were found from frontal and parietal/occipital sensor clusters, with young subjects having the strongest average amplitude, middle-aged subjects having intermediate average amplitudes, and old subjects having the weakest average amplitude (see Figure 3).

Age differences of P300 topography correlation coefficients were found, $F_{2,96}$=5.08, p=.01, with young subjects (R=.80 +/- .05) having a larger topography correlation than old subjects (R=.57 +/- .05); no differences were found between young and middle-aged subjects (R=.66 +/- .05) or between middle-aged and old subjects (see Figure 4). The differences between young and old subjects indicate that the young subjects had smaller individual variability of P300 scalp topography distributions than old subjects; the grand average P300 topography for old subjects was not representative of individual subjects' P300. Subgroups of non-representative middle-

aged (n=5) and old subjects (n=7) had r values smaller than individual young subjects' minimum r value (r=.59). Their P300 topography distributions were shown in Figure 5. Representative subjects of both age groups had stronger P300 than non-representative subjects; this difference was especially salient among old subjects. OSPAN scores were also compared between the representative and non-representative subjects. For middle-aged subjects, no subgroup differences were found (t_9=2.06, p=.07). For old subjects, however, representative subgroup (25^{th} percentile=14.00, median=16.00, 75^{th} percentile=20.00) had a higher average OSPAN rank than non-representative group (25^{th} percentile=7.5, median=9.00, 75^{th} percentile=9.00), t_8=3.60, p=.01.

OSPAN score. Significant age differences were found on OSPAN scores, $\chi^2_{2,34}$=22.96, p<.001. Young (25^{th} percentile=14.5, median=18, 75^{th} percentile=20.75) and middle-aged (25^{th} percentile=12.25, median=19.5, 75^{th} percentile=24) subjects had a higher average OSPAN rank score than old subjects (25^{th} percentile=9.00, median=14.00, 75^{th} percentile=18.25). No differences were found between young and middle-aged subjects (see Figure 6).

OSPAN Rank Effects

N100. A significant OSPAN rank effect was found for N100 latency, $F_{2,96}$=3.38, p=.04. Low OSPAN subjects (104.92 +/- 1.73 ms) had longer N100 latency than median (99.54 +/- 1.23 ms) and high OSPAN subjects (100.17 +/- 1.80 ms). No difference existed between median and high OSPAN subjects. No stimuli type effects ($F_{1.96}$=3.75, p=.06) or interactions ($F_{2,96}$=0.10, p=.90) between the two factors were found (see Figure 7). OSPAN rank differences of N100 amplitude were found from one right parietal sensor cluster, with low OSPAN subjects having the weakest average amplitude, median OSPAN subjects having the intermediate average amplitude, and high OSPAN subjects having the strongest average amplitude (see Figure 8). Auditory stimuli type effects were also found from one frontal sensor cluster, with standard stimuli having weaker

average amplitude than target stimuli, see Figure 2. No OSPAN rank differences ($F_{2,96}$=1.41, p=.25) or stimuli type effects ($F_{1.96}$=0.31, p=.58) were found on N100 topography correlation coefficients, indicating that the OSPAN rank groups had similar individual variability of N100 scalp topography distributions; the average N100 topography was representative of individual subjects' N100.

P200. No OSPAN rank differences of P200 latency were found ($F_{2,48}$=1.24, p=.30). OSPAN rank differences of P200 amplitude were from one frontal sensor cluster, with low OSPAN subjects having the weakest average amplitude, median OSPAN subjects having intermediate amplitudes, and high OSPAN subjects having the strongest average amplitude (see Figure 9). No OSPAN rank differences ($F_{2,96}$=0.08, p=.92) were found on P200 topography correlation coefficients; indicating that the OSPAN rank groups had similar individual variability of P200 scalp topography distributions; the average P200 topography was representative of individual subjects' P200.

N200. No OSPAN rank differences of N200 latency were found ($F_{2,48}$=0.29, p=.75). OSPAN rank differences of N200 amplitude were found from one frontal sensor cluster, with low OSPAN subjects having the weakest average amplitude, median OSPAN subjects having intermediate amplitudes, and high OSPAN subjects having the strongest average amplitude (see Figure 9). No OSPAN rank differences ($F_{2,96}$=0.22, p=.80) were found on N200 topography correlation coefficients, , indicating that the OSPAN rank groups had similar individual variability of N200 scalp topography distributions; the average N200 topography was representative of individual subjects' N200.

P300. Significant OSPAN rank differences were found for P300 latency, $F_{2,48}$=4.04, p=.02. Low OSPAN subjects (420.92 +/- 18.46 ms) had longer P300 latency than median (360.38 +/-

13.05 ms) and high OSPAN subjects (359.67 +/- 19.21 ms). No differences were found between median and high OSPAN subjects (see Figure 7). OSPAN rank differences of P300 amplitude were found from one frontal sensor cluster, with low OSPAN subjects having the weakest average amplitude, median OSPAN subjects having intermediate amplitudes, and high OSPAN subjects having the strongest average amplitude (see Figure 9). No OSPAN rank differences ($F_{2,96}$=0.97, p=.39) were found on P300 topography correlation coefficients, indicating that the OSPAN rank groups had similar individual variability of P300 scalp topography spatial distributions; the average p300 topography was representative of individual subjects' P300.

Chapter 4 Discussion

In general, our findings indicate that the normal aging of human brain does play an important role in altering cortical neural activations. These brain response alternations are related to age-associated cognitive differences, especially those contributing to sensory processes and working memory. The functional implications of those differences are discussed below.

Altered Cortical Activations during Sensory Processes

The earlier N100 and P200 index sensory processes. They are sensitive to bottom-up influences, i.e. features of sensory stimuli, such as pitch of sound and stimuli occurring frequencies in an oddball paradigm (Näätänen & Picton, 1987; Teder, et al., 1993; Woldorff et al., 1993) and top-down influences, i.e. attention and memory, regulatory modulations (Clementz et al., 2002; Huotilainen et al., 1998). Longer ERP latency and weaker ERP strength are associated with a lower degree of cortical neural responsiveness or excitability (Dustman et al., 1990; Cohen et al., 1995; Maeshima, Okita, Yamaga, Ozaki, & Moriwaki, 2003; Missonnier et al., 2007; Scisco, Leynes, & Kang, 2008). The three age groups differed significantly on ERP latencies, strength, and topographic correlations.

N100. N100, the earliest scalp potential identified in our experiment, carries two major effects, i.e. age differences and stimuli type effects (see Figure 2). Consistent with a number of previous studies addressing age-associated differences on the magnitude of scalp recorded auditory ERP and/or event-related magnetic field (Anderer et al., 1996; Chao & Knight, 1997; Ford & Pfefferbaum, 1991; Gao et al., 2007; Polich, 1997), we found that young subjects had the weakest N100; middle-aged subjects had the intermediate N100; old subjects had the strongest N100. Further analyses of OSPAN rank effects reveal that for all age groups, subjects with lower OSPAN scores had N100 with longer latencies and weaker strength (see Figure 8), which is

consistent with the results from previous studies investigating the relationship between OSPAN performance and ERP measures (Nittono et al., 1999).

Our findings suggest that normal aging is not the only factor contributing to neural activity alternations; individual differences of working memory capacity also play an important role. First, stronger N100 in middle-aged and old subjects agrees with the observations that older adults not only have poorer behavioral performance in sound intensity discrimination threshold tasks but also demonstrate larger N100 than young adults (Harris, Mills, & Dubno, 2007). Aged animals have decreased GABAergic inhibitory regulations in primary sensory cortices. The enhanced N100 strength in our study can be attributed to an age-associated reduction of cortical inhibitory control (Ling et al., 2005). Second, subjects with higher OSPAN scores are known to have ERPs with shorter latency and larger amplitude (Nittono et al., 1999), suggesting that some middle-aged and old subjects still retain sensory functional capacities to have the same cortical activations as young adults.

Stimuli type effects analyses reveal that regardless of age differences and OSPAN rank effects, N100 evoked by standard stimuli had weaker strength than N100 evoked by target stimuli. The stronger N100 didn't seem to adversely interfere with middle-aged and old subjects' sensory cortices' function to separate standard from target stimuli. The high topography correlations of N100 for all three age groups reinforce the notion that middle-aged and old subjects' sensory cortices still retain some degrees of functional competence (see Figure 4).

P200. P200 is the next ERP following N100. P200 is affected by bottom-up factors; it also carries a larger proportion of top-down regulatory modulations than N100 (Golob & Starr, 2000). In current study, P200 evoked by standard stimuli is identified from all age groups; P200 evoked by target stimuli is only observed among old subjects.

P200 evoked by standard stimuli carries age differences. Young subjects' P200 occurred earlier than middle-aged and old subjects' P200. Strength of P200 varied with age: young subjects had the weakest P200; middle-aged subjects had the intermediate P200; old subjects had the strongest P200. In addition, young subjects had lower within age group topography similarity than middle-aged and old subjects (see Figure 4). Analyses of the OSPAN rank effects reveal that for all age groups, subjects with lower OSPAN scores had P200 with longer latencies and weaker strength (see Figure 8).

Age differences of P200 latency and strength seem to be contradictory. Young subjects' shorter P200 latency indexes superior neural responses; their weaker P200 strength represents lower degrees of neural activations, and vice versa for middle-aged and old subjects. The contradiction is self-explaining when taking account of N100's age differences. Young subjects' faster and weaker P200 suggests that their neural circuitry responds to sensory stimuli more efficiently with proper inhibitory control. The stronger P200 in middle-aged and old subjects is likely to be a continuum the stronger N100. Their overexcited neural circuitries in primary auditory cortex carry the extra amount of neural activations from N100, triggering the sequential stronger P200. The prolonged P200 latencies are the temporal lags for additional neural activations associated with sensory processes.

Although P200 topography correlations also carry age differences, the higher values suggest that the average P200 for each age group did represent individual subjects' topography. Young subjects' larger individual variability of P200 topography may be explained by the fact that their non-overexcited sensory cortices have larger degrees of freedom to respond to sensory stimuli with more spatial topography patterns. Middle-aged and old subjects' smaller P200 topographic

variability may result from the overexcitement so that their sensory circuitries can only respond to the extra amount of neural signaling with limited degrees of freedom.

Another set of interesting and critical findings is the stimuli type effects of old subjects' P200. Old subjects were slower in response to standard than target stimuli. P200 strength did not differ. Old subjects' P200 evoked by standard stimuli also had smaller topography variability than P200 evoked by target stimuli. The latency and topography correlation differences suggest that old subjects' sensory cortices still preserve the functional competence to separate standard and target stimuli. The unique presence of P200 in response to target implies that although old subjects' sensory cortices remain functionally competent, their activations in response to target are similar as to standard stimuli.

Normal Aging Associated Working Memory Functional Alternations

N200. All age groups had N200 only in response to target stimuli. The association of N200 with target stimuli suggests that it is an ERP related to target identification. Young subjects' N200 occurred earlier than middle-aged and old subjects' N200. One intriguing age difference is that, unlike N100 or P200, young subjects had the strongest N200; middle-aged subjects had the intermediate N200; old subjects had the weakest N200.

Prior to N200, all age groups had N100 in response to target stimuli. Middle-aged and old subjects' stronger N100 suggest that their sensory cortices were "exhausted" by the overexcitement from the reduced cortical inhibitory modulations. The neural exhaustion compromised their sensory cortices' responsive capacity to generate a comparable N200 as seen in young subjects.

Age differences of P300. P300 evoked by target stimuli was identified from all age groups. Young and middle-aged subjects' P300 occurred earlier than old subjects' P300. Young subjects

had the strongest P300; middle-aged subjects had the intermediate P300; old subjects had the weakest P300.

Two possible mechanisms can account for the age differences of P300. First, middle-aged and old subjects' weaker P300 amplitude suggests that their cortices have compromised functional capacity for efficient contextual updating. P300 is known to reflect an active mental model consolidation or environment context revision. If sensory stimuli deliver information that mismatches the environment context or is useful to maintain memory representation of the environment, subjects' mental models are updated. P300 is preceded by the sensory evaluations for later memory updating (Klein, Coles, & Donchin, 1984). Middle-aged and old subjects' stronger N100 and weaker N200 suggest their sensory cortices were unable to evaluate sensory stimuli efficiently. Even their neural circuitries generating P300 could still remain functionally intact; the preceding alternations in stimuli evaluation processes can eventually lead to compromised working memory contextual updating.

Second, normal aging can affect the subcortical and cortical neural circuitries generating P300. Age-associated neuron loss, decreased neurotransmitter syntheses, abnormal neural firing rates, and reduced cortical synaptic innervations are very likely to affect middle-aged and old subjects' neural circuitries (Ishida, Shirokawa, Miyaishi, Komatsu, & Isobe, 2001; Manaye, Mclntire, Mann, & German, 1995; Shibata et al., 2006), which can lead to altered cortical P300 in response to target stimuli (Aston-Jones, Rajkowski, & Cohen, 1999; German, Nelson, Liang, Liang, & Games, 2005; Grudzien et al., 2007). For instance, the reduced LC norepinephrine (NE) activity can impair aged monkeys' performance in delayed response task. This impairment can be reversed directly by injecting NE agonist into LC, which is attributed to an attenuation of

irrelevant stimuli distraction induced by the increased NE activity in LC. Conversely, distraction is magnified whenever NE activity is reduced in LC (Coull, 1994).

The functional implication of P300 age differences is an individualized combination of the two possible mechanisms. Normal aging increases older subjects' neural circuitry response variability. Young subjects' average P300 is more representative of individual young subjects than middle-aged and old subjects' average P300. The larger topography individual variability among old subjects (see Figure 5) suggest that the two mechanisms accounting for P300 age differences can weight differently for each old individual. For instance, the compromised contextual updating process by itself can lead to altered P300 with intact neural circuitries; a combination of the compromised working memory updating together with the altered neural circuitries can also lead to similar results.

In summary, normal aging can alter middle-aged and old subjects' cortical activation dynamics, so that neither group is capable of generating a comparable P300 as seen in young subjects. The differences between middle-aged and old subjects can be accounted by the fact that old subjects sufferred more from normal aging induced changes than middle-aged subjects.

Age differences of OSPAN test. All subjects in our study sample had comparable cognitive abilities assessed by the MMSE and WAIS-III information subscale. The differences observed in the OSPAN tasks, therefore, are attributed to working memory capacity variations.

In OSPAN test, subjects first applied task-specific arithmetic processes to an equation, then added a word to working memory, then processed the second equation while maintaining the working memory load, then updated working memory with the second word, and so on. This cycle required switching between tasks-specific processes and working memory updating (Turner & Engle, 1989; Unsworth et al., 2005). Age differences of working memory captured by

subjects' OPSAN performance are consistent with other psychometric measurements (Emery, Hale, & Myerson, 2008; Goffaux, Phillips, Sinai, & Pushkar, 2008). Old subjects' lower OSPAN scores imply their compromised working memory capacity, which agrees with the fact that old adults often display difficulties in abstraction, planning, and the tendency to perseverate to a given response pattern (Fristoe, Salthouse, & Woodard, 1997).

Another intriguing finding is that old subjects with smaller P300 topography correlations also had significant lower OSPAN scores than old subjects with higher correlations. Topography similarity represents the degrees of individual P300 variability. It is very likely that the impact of normal aging on working memory (both cortical activations and behavioral performance) is greater among old subjects with lower OSPAN scores and smaller topography correlations. Analyses of OSPAN rank effects reveal that regardless of age groups, individuals with higher OSPAN scores had P300 with shorter latency and stronger amplitude, which is consistent with previous study (Nittono et al., 1999).

The conjunction of age differences on P300 and OSPAN scores supports the notion that normal aging does affect individuals' working memory but individual variability of working memory capacity also contributes to cortical activation differences.

Summary of Functional Implications

The altered ERPs during the earlier sensory processes, i.e. N100 and P200, are attributed to an age associated reduction of cortical inhibitory control; the altered later ERPs associated with working memory, i.e. N200 and P300, are attributed to a combination of two possible mechanisms, i.e. the compromised contextual updating due to the inefficient sensory stimuli evaluations and the aging induced changes of neural circuitries generating P300. Middle-aged and old subjects' smaller N200 and P300 do not agree with the HAROLD model, which refers to

older adults with superior tasks performances among their peers. Although our sample of middle-aged and old subjects did have a high target counting accuracy rate in oddball paradigm, the simplicity of task requirement make it unable to distinguish individuals with different working memory abilities. The age differences in OSPAN test reveal that our subject sample consists of older adults with low performance level; they are a heterogeneous group as compared to the subjects sample in the HAROLD model.

All together, our findings are in favor of an increased likelihood of normal aging associated cortical neural network re-organizations, which can eventually result in behavioral performance differences among older adults.

Chapter 5 Conclusions

Current experiment significantly extends previous studies investigating the effects of normal aging. Our subject sample demonstrates an age-associated ERPs (N100 and P200) latency and/or strength alternations during sensory processes, which is attributed to an overexcitement of sensory neural circuitry, leading to inefficient cortical activation in advanced age. Later ERP (N200 and P300) is characterized with an age-associated latency prolongation and strength weakening, which is attributed to the compromised sensory evaluations and/or age-associated alterations of neural circuitries generating cortical P300. Age differences revealed by ERPs are highly likely to be the neural mechanisms for compromised behavioral performance, which supports the mechanism of the aging induced cortical neural network re-organization rather than compensatory activations.

Our findings provide new evidence that ERP alternations in middle-aged subjects have similar characteristics as old subjects but with a reduced level of "age impact", suggesting that normal aging can start to impact individual's cortical sensory and working memory processes as early as in middle-age. More importantly, the current study demonstrate the advantage of combining P300 and OSPAN assessment, i.e. old subjects' low OSPAN scores coincide with their prolonged P300 latencies and attenuated P300 strength, which further confirms that P300 indexes working memory performance.

The current study also has limitations. For example, our subjects sample only include middle-aged and old subjects with lower OSPAN performance, leaving out the higher performers. A refined study can be used to pinpoint the mechanisms for P300 age differences with more specified sub-samples of middle-aged and old subjects based upon the OSPAN score distributions and the P300 topography.

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APPENDICES

APPENDIX A

UNIVERSITY OF GEORGIA
Department of Psychology
Consent to Act as a Research Subject
"EEG/MEG Studies of Rapid Auditory Processing in Aging"

Dr. Brett Clementz is conducting a research study to learn more about the relationship between brain functioning and aging. We hope to learn what effects aging has on the brain's ability to process information. You have been asked to participate because you have no known brain injury or psychiatric problems. There will be approximately 54 participants at this site.
If you decide to participate in this study, the following will happen:

1. You will be asked to fill out questionnaires and to answer questions asked by a researcher about past history or difficulties you may have had, which will last about an hour. All information is kept completely confidential.
2. You will be asked to complete a test called "operation-word-span (OSPAN)". This entails reading and verifying a simple math problem (such as (4/2)-1=1) to which you will answer "yes" or "no". You will read a word after the math operation (such as 'SNOW'). After a series of math problems and words have been presented, you will be asked to recall the words that followed each math operation.
3. Electroencephalography (EEG) will be used to record signals coming from your brain. This will involve sitting quietly in a comfortable chair. A cap with the EEG sensors will be placed on your head. The cap will cover the top of your head, leaving a clear field of vision. The procedure is not painful or invasive.
4. Magnetoencephalography (MEG) will also be used to record signals coming from your brain. This too will involve sitting quietly in a comfortable chair. Your head will be placed in a helmet that contains the MEG sensors. The helmet will cover your head from above your ears in the back and above your eyebrows in the front. The procedure is not painful or invasive.
5. While your brain activity is being recorded by the EEG and/or MEG, you will hear a variety of tones for about one hour. These tones will be presented through headphones. The task will be neither painful nor irritating. You can ask to stop at any time.
6. The total time commitment for this study is 2 hours.

Participation in this study may include the following risks or discomforts:

1. You may find some of the questions embarrassing. You will be asked questions about drug and alcohol use. You may refuse to answer any question.
2. There are no known harmful effects associated with any aspect of brain wave recording, which is totally noninvasive.

You will receive course credit or monetary compensation ($15/hour) for participating in this experiment. There are no other direct benefits from these procedures.

Research records will be kept confidential to the extent provided by the law. Information you provide during the initial session will be kept in a locked file cabinet, and names will be deleted from the files at the conclusion of the study. Data collected during MEG and EEG will be stored using a unique subject identification number only. No information about you, or provided by you

during the research, will be shared with others without your written permission, except if it is necessary to protect your welfare (for example, if you were injured and need physician care) or if required by law.

_____ has explained this study to you and answered your questions. If you have other questions, you may reach Dr. Clementz at (706) 542-4376.

Participation in research is entirely voluntary. You may refuse to participate or withdraw without penalty at any time.

I understand that I am agreeing by my signature on this form to take part in this research project and that I will receive a copy of this consent form for my records.

_____	_____	_____
Name of Researcher	Signature	Date

Telephone: _____
Email: _____

_____	_____	_____
Name of Participant	Signature	Date

Please sign both copies, keep one and return one to the researcher.
Additional questions or problems regarding your rights as a research participant should be addressed to The Chairperson, Institutional Review Board, University of Georgia, 612 Boyd Graduate Studies Research Center, Athens, Georgia 30602-7411; Telephone (706) 542-3199; E-Mail Address IRB@uga.edu.

APPENDIX B

try this: Best Practices in Nursing Care to Older Adults
from The Hartford Institute for Geriatric Nursing

Issue Number 3, January 1999 Series Editor: Meredith Wallace, PhD, RN, MSN, CS

The Mini Mental State Examination (MMSE)

By: Lenore Kurlowicz, PhD, RN, CS and Meredith Wallace, PhD, RN, MSN

WHY: Cognitive impairment is no longer considered a normal and inevitable change of aging. Although older adults are at higher risk than the rest of the population, changes in cognitive function often call for prompt and aggressive action. In older patients, cognitive functioning is especially likely to decline during illness or injury. The nurses' assessment of an older adult's cognitive status is instrumental in identifying early changes in physiological status, ability to learn, and evaluating responses to treatment.

BEST TOOL: The Mini Mental State Examination (MMSE) is a tool that can be used to systematically and thoroughly assess mental status. It is an 11-question measure that tests five areas of cognitive function: orientation, registration, attention and calculation, recall, and language. The maximum score is 30. A score of 23 or lower is indicative of cognitive impairment. The MMSE takes only 5-10 minutes to administer and is therefore practical to use repeatedly and routinely.

TARGET POPULATION: The MMSE is effective as a screening tool for cognitive impairment with older, community dwelling, hospitalized and institutionalized adults. Assessment of an older adult's cognitive function is best achieved when it is done routinely, systematically and thoroughly.

VALIDITY/RELIABILITY: Since its creation in 1975, the MMSE has been validated and extensively used in both clinical practice and research.

STRENGTHS AND LIMITATIONS: The MMSE is effective as a screening instrument to separate patients with cognitive impairment from those without it. In addition, when used repeatedly the instrument is able to measure changes in cognitive status that may benefit from intervention. However, the tool is not able to diagnose the case for changes in cognitive function and should not replace a complete clinical assessment of mental status. In addition, the instrument relies heavily on verbal response and reading and writing. Therefore, patients that are hearing and visually impaired, intubated, have low English literacy, or those with other communication disorders may perform poorly even when cognitively intact.

MORE ON THE TOPIC:

Folstein, M., Folstein, S.E., McHugh, P.R. (1975). "Mini-Mental State" a Practical Method for Grading the Cognitive State of Patients for the Clinician. *Journal of Psychiatric Research,* 12(3); 189-198.

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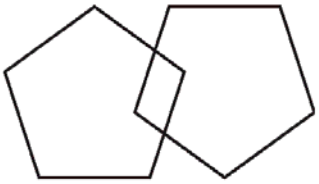
The Mini-Mental State Exam

Patient_____ Examiner _____ Date_____

Maximum	Score	
		Orientation
5	( )	What is the (year) (season) (date) (day) (month)?
5	( )	Where are we (state) (country) (town) (hospital) (floor)?
		Registration
3	( )	Name 3 objects: 1 second to say each. Then ask the patient all 3 after you have said them. Give 1 point for each correct answer. Then repeat them until he/she learns all 3. Count trials and record. Trials _____
		Attention and Calculation
5	( )	Serial 7's. 1 point for each correct answer. Stop after 5 answers. Alternatively spell "world" backward.
		Recall
3	( )	Ask for the 3 objects repeated above. Give 1 point for each correct answer.
		Language
2	( )	Name a pencil and watch.
1	( )	Repeat the following "No ifs, ands, or buts"
3	( )	Follow a 3-stage command: "Take a paper in your hand, fold it in half, and put it on the floor."
1	( )	Read and obey the following: CLOSE YOUR EYES
1	( )	Write a sentence.
1	( )	Copy the design shown.



_____ Total Score

ASSESS level of consciousness along a continuum _____

Alert Drowsy Stupor Coma

"MINI-MENTAL STATE." A PRACTICAL METHOD FOR GRADING THE COGNITIVE STATE OF PATIENTS FOR THE CLINICIAN. *Journal of Psychiatric Research*, 12(3): 189-198, 1975. Used by permission.

try this: Best Practices in Nursing Care to Older Adults

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The Hartford Institute for Geriatric Nursing
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Normative Data of MMSE

Cognitive performance as measured by the MMSE varies within the population by age and educational level. There is an inverse relationship between MMSE scores and age, ranging from a median of 29 for those 18 to 24 years of age, to 25 for individuals 80 years of age and older. The median MMSE score is 29 for individuals with at least 9 years of schooling, 26 for those with 5 to 8 years of schooling, and 22 for those with 0 to 4 years of schooling. The results in the following table (from Crum et al., 1993) can be used to compare your patient's MMSE score with those determined from a population reference group based on age and educational level.

	Age													
Education	**18-24**	**25-29**	**30-34**	**35-39**	**40-44**	**45-49**	**50-54**	**55-59**	**60-64**	**65-69**	**70-74**	**75-79**	**80-84**	**>84**
4th grade	22	25	25	23	23	23	23	22	23	22	22	21	20	19
8th grade	27	27	26	26	27	26	27	26	26	26	25	25	25	23
High School	29	29	29	28	28	28	28	28	28	28	27	27	25	26
College	29	29	29	29	29	29	29	29	29	29	28	28	27	27

APPENDIX C

WAIS-II

Directions for Administration and Scoring

DIRECTIONS: Start with item 5 and give credit for items 1-4 if the subject passes *both* items 5 and 6. If either 5 or 6 is failed, administer items 1-4 before preceding further.

Read each question exactly as stated. If the response to a question is incomplete or not clear, you must say,

Explain what you mean or tell me more about it,

but do not ask leading questions or spell the words. Do not alter the wording of any question.

Record, verbatim, the subject's response to each item in the appropriate space on the Record form.

DISCONTINUE after 5 consecutive failures.

SCORING 1 point for each correct response. Essentials of acceptable answers are noted below. Where several acceptable answers are listed (separated by three dots), the subject need give only one to receive credit.

Maximum Score: 29 points

Test Questions	Acceptable Answers
1. What are the colors in the American Flag?	Red, white and blue.
2. What is the shape of a ball?	Round
3. How many months are there in a year?	12
4. What is a thermometer?	Instrument (thing, etc.) for measuring temperature.
5. Where does the sun rise?	In the East. (if the points, say, **Yes, but what direction is that?**)
6. Name four men who have been the president of the United States since 1950.	Truman, Eisenhower, Kennedy, Johnson, Nixon, Ford, Carter, Reagan, Bush, Clinton, Bush

7. How many weeks are there in a year?	52
8. Who was Louis Armstrong? ("Louis" should be pronounced "Louie.")	Musician…Trumpet player… Singer…Entertainer…Band leader. (If the subject gives some other correct answer such as "Satchmo", say, **but what is he most famous for?**)
9. In what direction would you travel if you went from Chicago to Panama?	South…Southeast…Southwest
10. In what month is Labor Day?	September
11. On what continent is Brazil?	South America
12. Who wrote Hamlet?	William Shakespeare… Shakespeare
13. Who was the president of the United States during the Civil War?	Abraham Lincoln…Lincoln
14. Who was Amelia Earhart? ("Earhart should be pronounced "Air-heart.")	Aviator…Flyer…Pilot. (Accept "First women pilot" as correct.)
15. Why are dark clothes warmer than light-colored clothes?	Dark clothes absorb heat from the sun…Light clothes reflect (repel) heat form the sun. (Do *not* give credit for response that dark clothes "hold," "attract," or "draw" heat.)
16. What is the capital of Italy?	Rome
17. Who was Martin Luther King?	Civil rights leader…Worker for poor people…Helped blacks stand up for their rights. (If the subject gives some other correct answer such as "Minister" or "Black leader," say, **But what is he most famous for?**)
18. What is the main theme of the book of Genesis?	Creation…Beginning of the world …Beginning of man…Early Hebrew History

19. In what continent is the Sahara Desert?	Africa
20. Whose name is usually associated with the theory of relativity?	Albert Einstein…Einstein
21. How does yeast cause do to rise?	It causes fermentation which produces carbon dioxide bubbles and make the dough swell…Gases are formed…It ferments…It expands…It forms air bubbles…Bacterial action. (Do *not* give credit for "Chemical reaction.")
22. How many senators are there in the United States Senate?	100
23. How far is it from paris to New York?	Any answer between 3000 and 4000 miles (or between 4800 and 6500 kilometers).
24. Name three kinds of blood vessels in the human body.	Arteries, veins, and capillaries. (Names of specific vessels are not acceptable, but give credit for venules and arterioles).
25. At what temperature does water boil?	212°F…100°C…373K. (If the scale is not specified, say, **What scale?**)
26. What was Marie Curie famous for?	Chemist…Physicist…Scientist… Discoverer if radium…Discovered radioactivity. (Do *not* give credit for "Discoverer of radiation.")
27. What is the population of the United States?	298,444,215 as of July 2006 (CIA) Any answer within 20%, in either direction of current population size.
28. What is the Koran?	Mohammedan scriptures… Mohammedan sacred writings… Mohammedan Bible. (Moslem or Islamic in place of Mohammedan is acceptable.)
29. Who wrote Faust?	Goethe…Gounod.

APPENDIX D

Operation span (OSPAN) practice and task trials

Practice trials

Task 1
IS (9 ÷ 3) – 2 = 2 ? AUNT
IS (8 ÷ 4) – 1 = 1 ? BUSH

Task 2
IS (6 ÷ 2) + 1 = 4 ? CORN
IS (6 x 3) – 2 = 11 ? BEAR

Task 3
IS (4 x 2) + 1 = 9 ? JAR
IS (10 ÷ 2) + 4 = 9 ? DECK

Testing trials

Task 1
IS (10 ÷ 2) - 3 = 2 ? SEA
IS (10 ÷ 10) - 1 = 2 ? CLASS
IS (7 ÷ 1) + 2 = 7 ? PAINT

Task 2
IS (3 ÷ 1) - 2 = 3 ? CLOUD
IS (2 x 1) - 1 = 1 ? PIPE
IS (10 ÷ 1) + 3 = 13 ? EAR
IS (9 x 2) + 1 = 18 ? FLAME
IS (9 ÷ 1) - 7 = 4 ? BIKE

Task 3
IS (8 x 4) - 2 = 32 ? BEAN
IS (9 x 3) - 3 = 24 ? ARM
IS (4 ÷ 1) + 1 = 4 ? GROUND

Task 4
IS (10 ÷ 1) - 1 = 9 ? HOLE
IS (8 x 4) + 2 = 34 ? DAD

Task 5
IS (6 x 3) + 2 = 17 ? KID
IS (6 ÷ 3) + 2 = 5 ? FORK
IS (6 x 2) - 3 = 10 ? JAIL

IS (8 ÷ 2) + 4 = 2 ? HAT
IS (8 ÷ 2) - 1 = 3 ? LAMP

Task 6
IS (9 ÷ 1) - 5 = 4 ? CAVE
IS (6 ÷ 2) - 2 = 2 ? BACK
IS (7 x 2) - 1 = 14 ? HALL
IS (6 x 2) - 2 = 10 ? FERN

Task 7
IS (2 x 2) + 1 = 4 ? MAN
IS (7 x 1) + 6 = 13 ? WORLD

Task 8
IS (3 ÷ 1) + 3 = 6 ? DRILL
IS (10 ÷ 1) + 1 = 10 ? CALF
IS (4 x 4) + 1 = 17 ? FISH
IS (3 x 3) - 1 = 8 ? CHEEK

Task 9
IS (3 x 1) + 2 = 2 ? BREAD
IS (4 ÷ 2) + 1 = 6 ? GERM
IS (5 ÷ 5) + 1 = 2 ? DOCK

Task 10
IS (2 x 3) + 1 = 4 ? GAME
IS (9 ÷ 3) - 2 = 1 NERVE
IS (10 ÷ 2) - 4 = 3 ? WAX
IS (5 ÷ 1) + 4 = 9 ? TIN
IS (10 x 2) + 3 = 23 ? CHURCH

Task 11
IS (7 ÷ 1) + 6 = 12 ? BEACH
IS (3 x 2) + 1 = 6 ? CARD

Task 12
IS (6 x 4) + 1 = 25 ? JOB
IS (9 ÷ 3) - 1 = 2 ? CONE
IS (8 ÷ 1) - 6 = 4 ? BRASS
IS (9 x 1) + 9 = 1 ? STREET

OSPAN answer sheet

SS#_____

Practice: Date_____

A			
B			
C			

Actual Task:

1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					

OSPAN answer keys

SS#_____

Practice: Date_____

A) □N (aunt) □Y (bush)
B) □Y (corn) □N (bear)
C) □Y (jar) □Y (deck)

Actual Task:

1.	□Y (sea)	□N (class)	□N (paint)	□	□
2.	□N (cloud)	□Y (pipe)	□Y (ear)	□N (flame)	□N (bike)
3.	□N (bean)	□Y (arm)	□N (ground)	□	□
4.	□Y (hole)	□Y (dad)	□	□	□
5.	□N (kid)	□N (fork)	□N (jail)	□N (hat)	□Y (lamp)
6.	□Y (cave)	□N (back)	□N (hall)	□Y (fern)	□
7.	□N (man)	□Y (world)	□	□	□
8.	□Y (drill)	□N (calf)	□Y (fish)	□Y (cheek)	□
9.	□N (bread)	□N (germ)	□Y (dock)	□	□
10.	□N (game)	□Y (nerve)	□N (wax)	□Y (tin)	□Y (church)
11.	□N (beach)	□N (card)	□	□	□
12.	□Y (job)	□Y (cone)	□N (brass)	□N (street)	□

Figure 1. Global field power (GFP) of ERPs separated by age groups. A 600 ms time window was used, with 100 ms pre-stimuli baseline and 500 ms post-stimuli response period. Figure in top panel is the GFP of standard stimuli; figure in the bottom panel is the GFP of target stimuli. Auditory event-related potentials (ERPs) were identified, i.e. N100 and P200 evoked by standard stimuli of three age groups; N100, N200, and P300 evoked by target stimuli of three age groups. Old subjects had an additional P200 component evoked by target stimuli. The latency of each ERP component was identified based upon their peak values in the GFP figures.

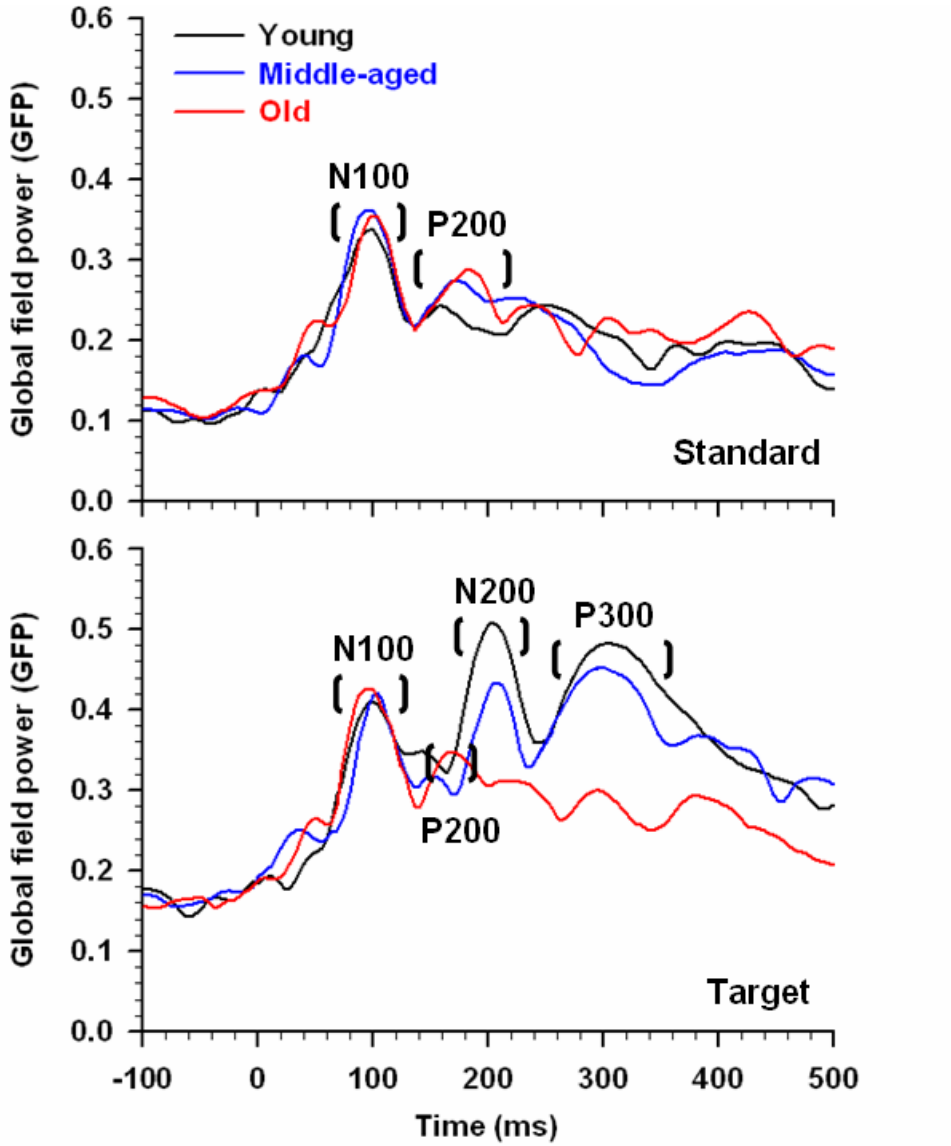
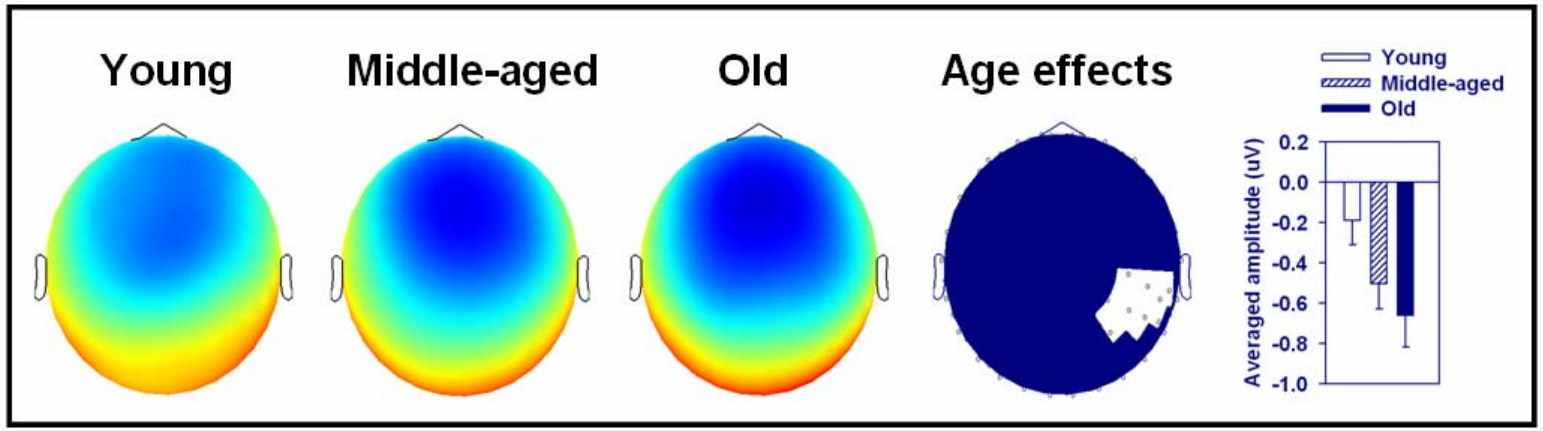

Young
Middle-aged
Old
N100
P200
Standard
N100
N200
P300
P200
Target
Global field power (GFP)
Global field power (GFP)
0.0
0.1
0.2
0.3
0.4
0.5
0.6
-100
0
100
200
300
400
500
Time (ms)

Figure 2. Age differences and stimuli type effects of N100 amplitude. Figures in the top panel demonstrate age differences of N100 amplitude (the averaged N100s evoked by standard and target stimuli); figures in the bottom panel demonstrate stimuli type effects of N100 (the averaged N100s across age groups) amplitude. Top-down projects of N100 scalp distribution are shown with the same colored scales. Warm color represents positive voltage values; cold color represents negative voltage values. The main effects of age differences/stimuli type from ANOVA analysis are shown as the blue-white scaled figures. Sensor clusters with significant age differences/stimuli type effects are white; sensor clusters without age differences/stimuli type effects are blue. The bar-graphs demonstrate the voltage values averaged from sensor clusters with significant age differences/stimuli type effects.


Young
Middle-aged
Old
Age effects
Young
Middle-aged
Old
Averaged amplitude (uV)
0.2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0

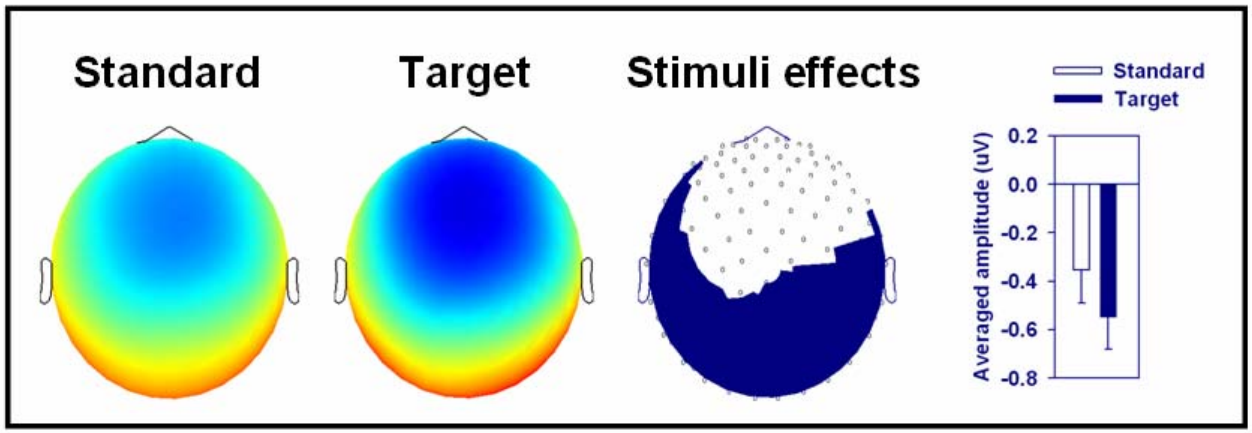

Standard
Target
Stimuli effects
Standard
Target
Averaged amplitude (uV)
0.2
0.0
-0.2
-0.4
-0.6
-0.8

Figure 3. Age differences of P200/N200/P300 amplitude. Figures in the top panel demonstrate age differences of P200 amplitude (evoked by standards stimuli); figures in the middle panel demonstrate age differences of N200 (evoked by target stimuli) amplitude; figures in the bottom panel demonstrate age differences of P300 (evoked by target stimuli) amplitude. Top-down projects of P200/N200/P300 scalp distribution are shown with colored scales (the same scale within component; different scales across components). Warm color represents positive voltage values; cold color represents negative voltage values. The main effects of age from ANOVA analysis are shown as the blue-white scaled figures. Sensor clusters with significant age differences are white; sensor clusters without age differences are blue. The bar-graphs demonstrate the voltage values averaged from sensor clusters with significant age differences.

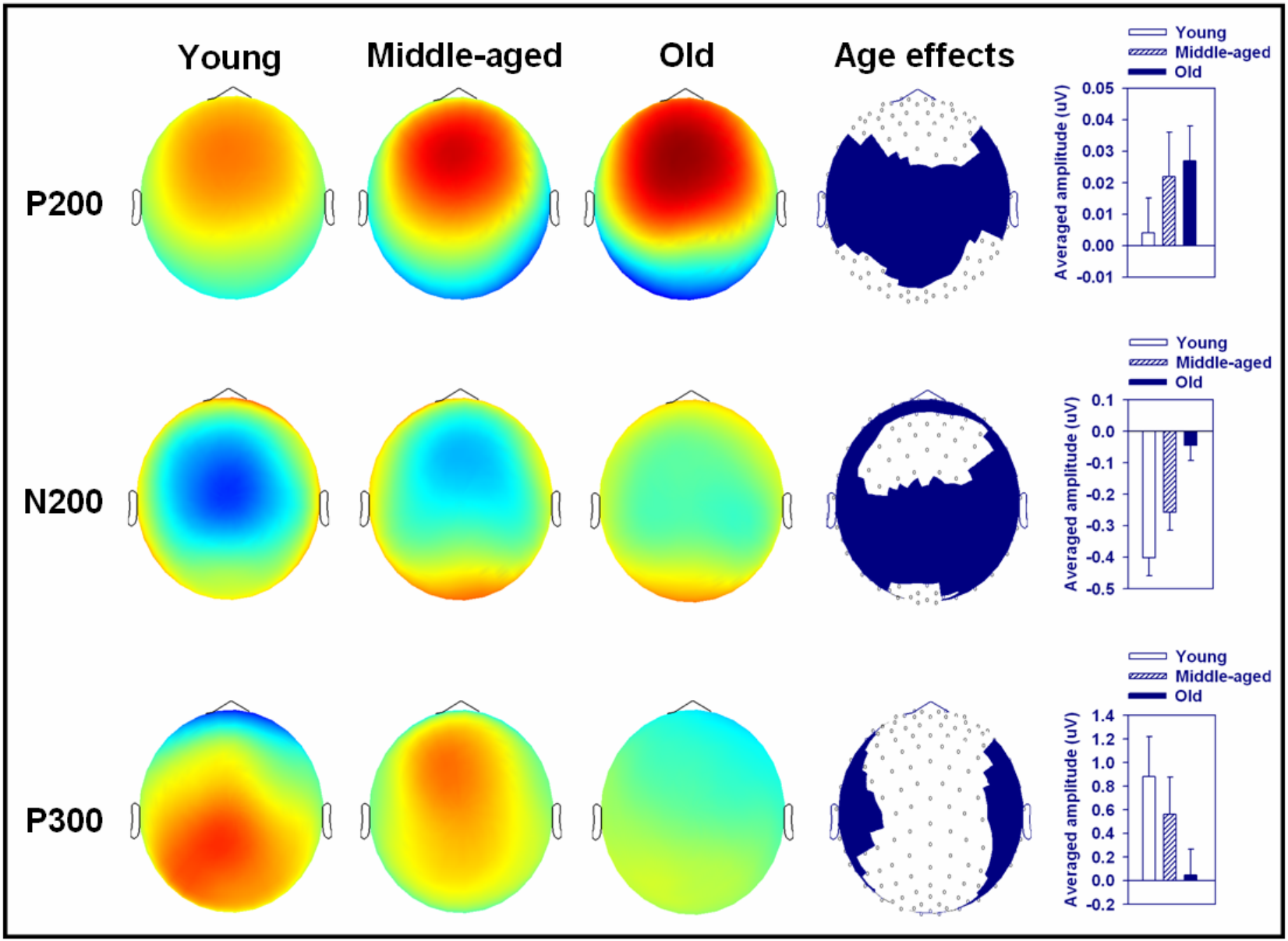

Young
Middle-aged
Old
Age effects
P200
N200
P300
Young
Middle-aged
Old
Averaged amplitude (uV)
0.05
0.04
0.03
0.02
0.01
0.00
-0.01
0.1
0.0
-0.1
-0.2
-0.3
-0.4
-0.5
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2

Figure 4. Topography correlation coefficients (r) of ERP components. Topographic correlations of N100, P200, N200, and P300 are separated by age groups and/or stimuli types. Topography correlations of N100 are averaged across stimuli types.

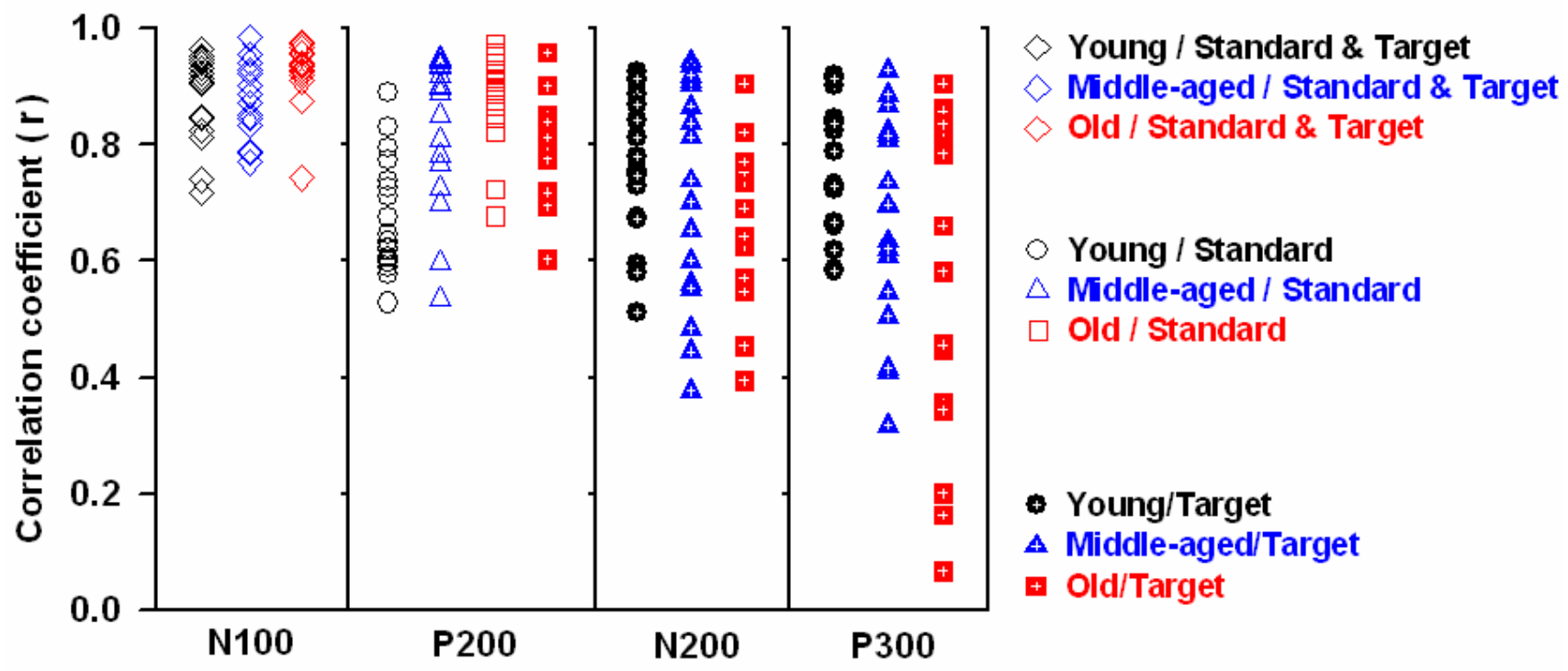

Correlation coefficient (r)
1.0
0.8
0.6
0.4
0.2
0.0
N100
P200
N200
P300
Young / Standard & Target
Middle-aged / Standard & Target
Old / Standard & Target
Young / Standard
Middle-aged / Standard
Old / Standard
Young/Target
Middle-aged/Target
Old/Target

Figure 5. Comparisons of subject with representative and non-representative P300 topographic distributions. The left panel shows the P300 topographic correlation coefficients (r) of three age groups. Middle-aged and old subjects' r values were divided into two subgroups, i.e. r values smaller than young subjects' minimum r value (a black horizontal cutoff line marks the minimum r value and the subgroups) were denoted as non-representative subjects; r values equal to or larger than young subjects' minimum r value were denoted as representative subjects. Top-down projections of P300 responses from representative and non-representative subjects were shown on the right panel for each age group with the same colored scales. Warm color represents positive voltage values; cold color represents negative voltage values.

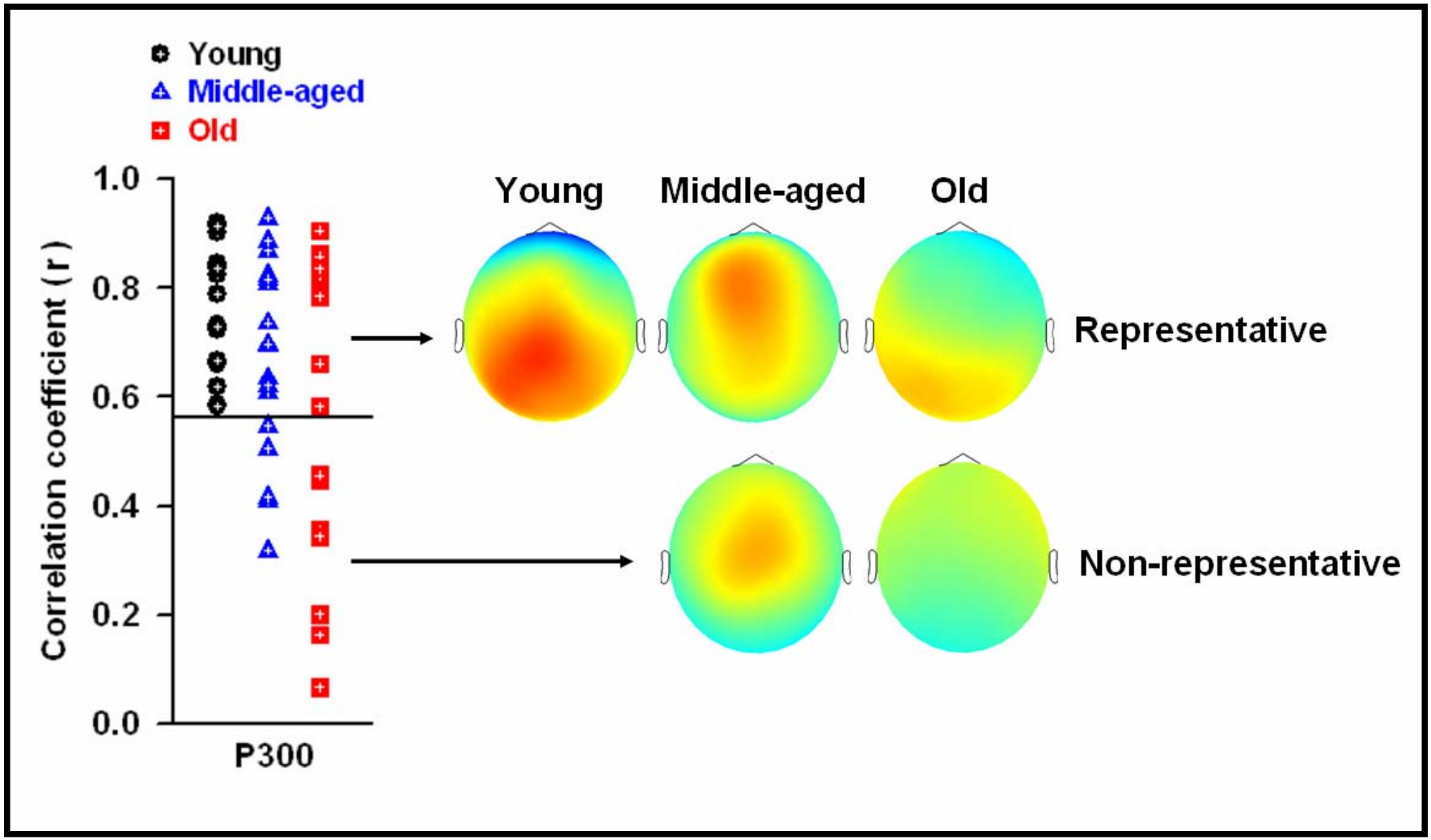

Young
Middle-aged
Old
Correlation coefficient (r)
1.0
0.8
0.6
0.4
0.2
0.0
P300
Young
Middle-aged
Old
Representative
Non-representative

Figure 6. OSPAN score distributions ranked in ascending order separated by age groups. A total of 51 subjects' OSPAN scores are shown. The top portion (OSPAN scores from 22 to 42, 12 subjects from three age groups) of the figure denotes high OSPAN group; the middle portion (OSPAN scores from 11 to 21, 26 subjects from three age groups) of the figure denotes median OSPAN group; the bottom portion (OSPAN scores from 0 to 10, 13 subjects from three age groups) denotes low OSPAN group.

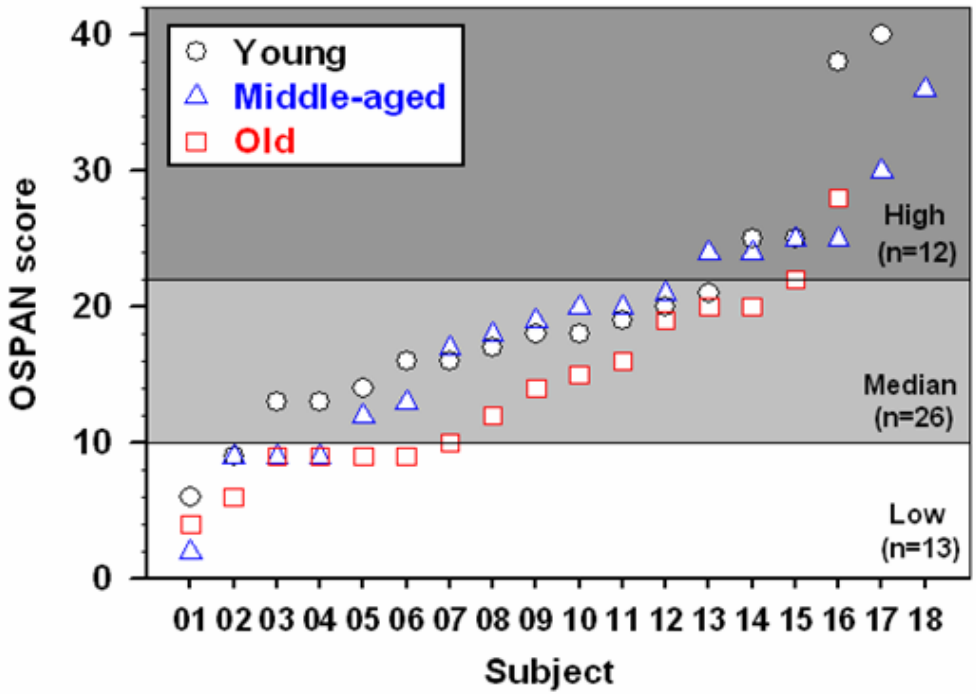

Young
Middle-aged
Old
High
(n=12)
Median
(n=26)
Low
(n=13)
OSPAN score
Subject
0
10
20
30
40
01 02 03 04 05 06 07 08 09 10 11 12 13 14 15 16 17 18

Figure 7. Global field power (GFP) of ERPs separated by OSPAN rank groups. A 600 ms time window was used, with 100 ms pre-stimuli baseline and 500 ms post-stimuli response period. The figure in top panel is the GFP of standard stimuli; the figure in the bottom panel is the GFP of target stimuli. Auditory event-related potentials (ERPs) were identified, i.e. N100 and P200 evoked by standard stimuli; N100, N200, and P300 evoked by target stimuli. The latency of each ERP component was identified based upon their peak values in the GFP figures.

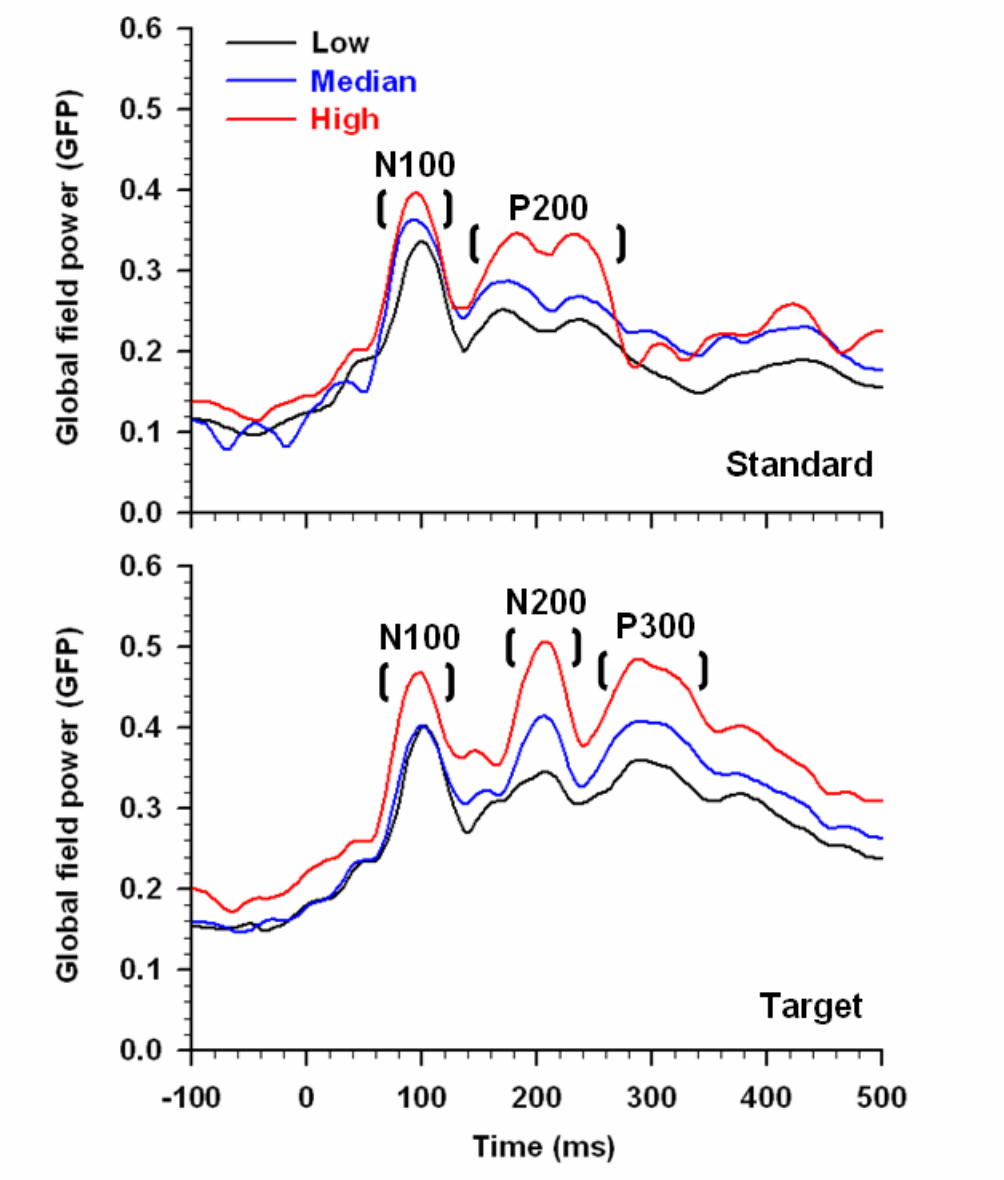

Low
Median
High
N100
P200
Standard
N100
N200
P300
Target
Global field power (GFP)
Global field power (GFP)
0.0
0.1
0.2
0.3
0.4
0.5
0.6
-100
0
100
200
300
400
500
Time (ms)

Figure 8. OSPAN rank differences and stimuli type effects of N100 amplitude. Figures in the top panel demonstrate OSPAN rank differences of N100 (the averaged N100s evoked by standard and target stimuli) amplitude; figures in the bottom panel demonstrate stimuli type effects of N100 amplitude. Top-down projects of N100 scalp distribution are shown with the same colored scales. Warm color represents positive voltage values; cold color represents negative voltage values. The main effects of OSPAN rank/stimuli type from ANOVA analysis are shown as the blue-white scaled figures. Sensor clusters with significant OSPAN rank differences/stimuli type effects are white; sensor clusters without OSPAN rank differences/stimuli type effects are blue. The bar-graphs demonstrate the voltage values averaged from sensor clusters with significant OSPAN rank differences/stimuli type effects.

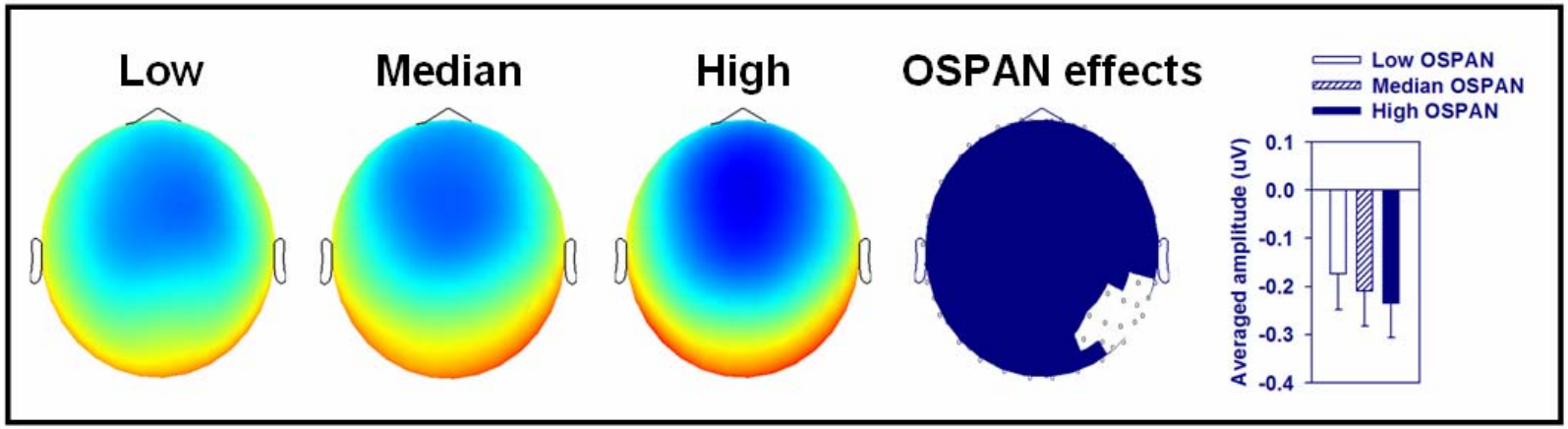
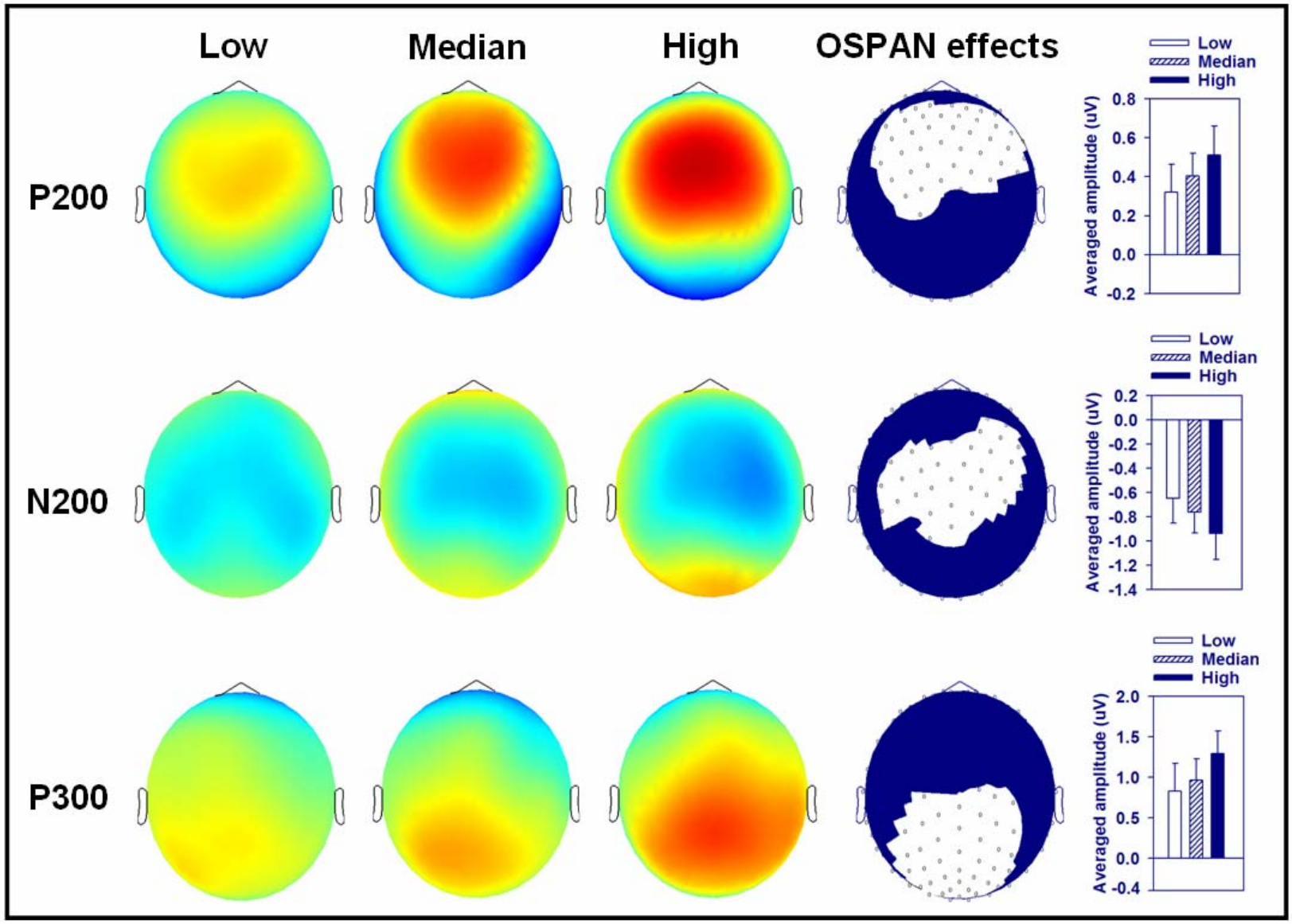

Low
Median
High
OSPAN effects
Low OSPAN
Median OSPAN
High OSPAN
Averaged amplitude (uV)
0.1
0.0
-0.1
-0.2
-0.3
-0.4

Figure 9. OSPAN rank differences of P200/N200/P300 amplitude. Figures in the top panel demonstrate OSPAN rank differences of P200 (evoked by standard stimuli) amplitude; figures in the middle panel demonstrate OSPAN rank differences of N200 (evoked by target stimuli) amplitude; figures in the bottom panel demonstrate OSPAN rank differences of P300 (evoked by target stimuli) amplitude. Top-down projects of P200/N200/P300 scalp distribution are shown with colored scales (the same scale within component; different scales across components). Warm color represents positive voltage values; cold color represents negative voltage values. The main effects of OSPAN rank from ANOVA analysis are shown as the blue-white scaled figures. Sensor clusters with significant OSPAN rank differences are white; sensor clusters without OSPAN rank differences are blue. The bar-graphs demonstrate the voltage values averaged from sensor clusters with significant OSPAN rank differences.


Low
Median
High
OSPAN effects
P200
N200
P300
Low
Median
High
Averaged amplitude (uV)
0.8
0.6
0.4
0.2
0.0
-0.2
0.2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
-1.4
2.0
1.5
1.0
0.5
0.0
-0.4