NORMAL AGING ASSOCIATED FUNCTIONAL ALTERNATIONS IN AUDITORY SENSORY AND WORKING MEMORY PROCESSING

by

YUAN GAO

(Under the Direction of Brett A. Clementz)

ABSTRACT

The purpose of the present study was to determine normal aging associated changes in brain functions during auditory sensory and auditory working memory processing by magneto-encephalography (MEG) measurement. Old and young participants were recruited from data recording. It is found that though there are no significant age associated differences in behavioral performance; normal aging associated brain activations differ between age groups. For brain activations in auditory sensory processing, though both age groups activate the same cortical regions and show a habituation pattern on stimulus rate effects, old participants have larger response magnitude and faster response speed than young participants. For brain activations in auditory working memory, old participants' brain responses are slower than young participants' and different cortical areas of two age groups are activated in the same experiment task. The possible underlying mechanisms of these normal aging associated brain responses differences are discussed further.

INDEX WORDS: Normal aging, Auditory, Sensory, Working memory, MEG

NORMAL AGING ASSOCIATED FUNCTIONAL ALTERNATIONS IN AUDITORY SENSORY AND WORKING MEMORY PROCESSING

by

YUAN GAO

B. S., Beijing Normal University, Beijing, China, 2003

A Thesis Submitted to the Graduate Faculty of The University of Georgia in Partial Fulfillment of the Requirements for the Degree

MASTER OF SCIENCE

ATHENS, GEORGIA

2006

NORMAL AGING ASSOCIATED FUNCTIONAL ALTERNATIONS IN AUDITORY SENSORY AND WORKING MEMORY PROCESSING

by

YUAN GAO

Major Professor: Brett A. Clementz

Committee: Jennifer E. McDowell
Leonard W. Poon

Electronic Version Approved:

Maureen Grasso
Dean of the Graduate School
The University of Georgia
May 2006

ACKNOWLEDGEMENTS

The present thesis would not be complete without the direction of Dr. Brett A. Clementz and the generous support of Institute of Gerontology at University of Georgia.

TABLE OF CONTENTS

Page

LIST OF TABLE

Page

LIST OF FIGURES

Page

1 Introduction

Aging can lead to normal and/or pathological neural changes in both peripheral and central auditory systems (CAS), and these changes may affect individuals' basic sensory and higher level cognitive functions [Lord et al, 2003]. In CAS, (including primary, secondary and associated auditory cortex), neural activities take place on a time scale of milliseconds in order to process external auditory information efficiently. Normal aging associated changes in CAS can affect the efficiency and accuracy of neural activities by slowing down the speed of auditory information processing. Thus, technique providing high temporal and spatial resolution, such as magneto-encephalography (MEG), will be the ideal tool to address this issue.

The present thesis focuses on normal aging associated macroscopic neural changes in CAS and how these changes affect old adults' auditory sensory processing and higher-level cognitive functions in auditory system (working memory in present thesis). These questions of interest will be assessed using MEG. In the following sections, (1) technical background of MEG; (2) normal aging associated structural and neurochemical changes on human cerebral cortex; (3) background knowledge of normal aging associated changes in auditory sensory processing and auditory working memory, and (4) hypotheses of present thesis, will be addressed, respectively.

1.1 Technical background of MEG

1.1.1 Origins of neural signals measured by MEG

The transformation of neurochemical activities to electro-magnetic signals that can be measured outside the scalp provides the basis for the noninvasive measurement of macroscopic neural activity. Neural activity is often associated with the generation of action potentials. An action potential is generated and it travels down an axon to its terminus, if a certain electrical

threshold is reached at the axon hillock (the place where the axon leaves the soma or cell body). At the terminus of an axon is a junction, called the synapse, which allows a pre-synaptic neuron to communicate with a post-synaptic neuron. When the action potential reaches its terminus at the synapse, neurotransmitters are released into the synaptic cleft, or the gap between pre- and post-synaptic neurons. When neurotransmitters bind with specialized receptors on the post-synaptic membrane, a chemical process is initiated and it begins the neural signaling process in the post-synaptic neuron.

Action potentials generate electrical signals that are too brief in time (lasting only a few milliseconds) to be measured non-invasively. The electrical signals generated at the post-synaptic membrane (called post-synaptic potentials), however, are of longer duration (up to tens of milliseconds, [Plonsey et al, 1995]), and are thought to be the primary source of neural signals that are measurable non-invasively [Speckmann et al, 1999]. The post-synaptic potential is comprised of a dipolar electrical response (with a leading positive pole and a trailing negative pole) with typical strength values around 20 fAm (femto-amperes, or 10^{-15} amperes). To be detectable outside the head non-invasively, dipole strength must be on the order of 10 nAm (nano-amperes, or 10^{-9} amperes). Thus, the synchronous activations of hundreds of thousands, perhaps even millions, post-synaptic neurons are required to make detection of neural activity possible using non-invasive methods.

Besides the number of activated neurons, other factors, including geometry of individual group of activated neurons and the spatial relations among these activated neural groups are also important for detecting post-synaptic potentials outside the scalp [Lewine et al, 1995]. First, these neurons must be oriented in the same direction, known as an open field configuration. Random orientation of neurons, known as closed field configuration, causes these electrical

signals to cancel locally due to vector summation. Second, strength of the measurable electro-magnetic signals drops off as the square of the distance from its source, e.g. a signal with magnitude of 160 fT* (fT: femto-Teslaa, measure of magnetic field strength) measured at sensors that are 1 cm from its source inside the brain, would be measured at only 10 fT if the sensors are 4 cm from the source. This means that most signals measured from MEG sensors around the scalp are probably coming from the cerebral cortex, the very outside layer of the brain. Seventy percent the cerebral cortex is composed of pyramidal cells, which are large neurons oriented perpendicular to the cortical surface [Williamson et al, 1990]. MEG signals measured from the brain, therefore, mostly come from pyramidal cells located in the cerebral cortex. Third, these pyramidal cells must be oriented tangentially along the MEG sensors to allow for their magnetic field to be detected (see Figure 1.1-b).

1.1.2 Technical basis of MEG

To study the function of human cerebral cortex *in vivo* with high temporal resolution requires the use of high-density (meaning many sensors) electro- and/or magneto-encephalography (MEG). MEG is a non-invasive brain imaging technique and its recording is made possible by the use of super-conducting quantum interference devices (SQUIDs). To retain the super-conducting properties, the MEG recording sensors are located in a dewar containing liquid helium at -269°C. During recording, the container holding the sensors is brought close to human subject's head (see Figure 1.1-a). The sensors through super conducting flux transformers capture the alternating magnetic fields generated by the activities of neurons in the cerebral cortex while subjects are engaged in experimental tasks. The recorded magnetic fields are on the order of tens of femto-Tesla in amplitude [Kaufman et al., 2003; Okada 2003].

MEG provides good spatial (5 mm) and excellent temporal (1 msec) resolution; it is an ideal tool to study neural activities on cerebral cortex in the time course of millisecond. The basis of auditory event-related magnetic field measurement is to take short time-locked segments (epochs) of MEG data in response to auditory stimuli and average them across identical experimental conditions. By doing so, the signal-to-noise ratio (SNR) of the data is increased because (1) the spontaneous physiological changes, DC offset drifts and other random noise (signals of none interest) in MEG signals are averaged out and (2) the signals of interest in the current experimental conditions are reserved. After data averaging, source localization techniques are applied to determine the location of cortical neural sources generating the MEG signals [Vrba et al, 2001].

1.1.3 Basis of source localization

Given the assumption that cortical neurons are activated, if the strength, location and orientation of an intracranial activated neural source are known, there is a unique pattern of the extracranial magnetic fields generated by this source. This is defined as the *forward problem* [Gençer et al, 2003]. However, the MEG measurement records spatiotemporal activations of large number of cortical neurons without *a prior* knowledge of the activated neural sources' strength, location or orientation. To infer the location, strength and orientation of the neuronal generators from the recorded magnetic fields is defined as the *inverse problem*, and it is known that there is no unique solution to this problem [Wang et al., 2003]. Source localization techniques are strategies that are used to find an anatomically and functionally reasonable solution for the inverse problem by providing *a prior* constraining modeling information. For instance, the neural generators recorded in a binaural auditory sensory experiment will be more likely located in auditory cortex at left and right temporal lobes.

The most simple and widely used source localization algorithm is the equivalent current dipole (ECD) modeling. ECD assumes the magnetic fields recorded at the surface can be accounted for by a single dipolar source [Scherg 1990]. The ECD modeling is reasonable only when the neural sources, which generate the magnetic fields on cerebral surface, have focal activation patterns and the number of possible sources can be estimated with sufficient accuracy. However, the problem with single ECD modeling is that the actual neural generators of the observed magnetic fields are extended distributions of currents on the cerebral cortex and these generators will change their strength, locations, and orientations within millisecond time periods as the neural activations evolve. In many cases, the ECD modeling is reliable enough for localizing short-latency evoked fields, such as somatosensory and auditory evoked fields, in which the location of the corresponding neural generators can be well defined. When the brain activation is associated with complex cognitive performances, the ECD model is not well suited. Models that overcome the limitations of ECD are proposed, such as MUSIC (which is a multiple dipoles scan method which allows the identification of sources when they are coexisting) and the distributed source modeling.

The distributed source estimation (in present thesis, L2 minimum norm modeling) models the brain activation from the measured signals in terms of a large number of neural generators (or sources) and it projects the recorded MEG data into the source space. The solution to the inverse problem provided by minimum norm estimation can be interpreted as mapping of the measured neural signals towards the source space in the absence of prior assumptions of the sources distribution [Uutela et al, 1999].

Although the spatial accuracy of source localizations are compromised when using minimum norm modeling in that the spatial extent of activity is 'blurred' over a larger surface area than is actually activated, with sufficiently dense sensor arrays, minimum norm estimation can identify distinct regions of cortical activity that are separated by 0.5 to 1 cm [Wang et al, 2003]. Thus, the minimum norm modeling is well suited for analyses of MEG data with multiple simultaneously activated sources, as is often the case in studies of complex brain activity such as attention and auditory working memory.

1.2 Structural and neurochemical changes in normally aged cerebral cortex

Human cerebral cortex is composed of billions of neurons and their supporting cells. Neurons transduct external signals into bioelectrical signals and perform inter-neuron communication and they form the gray matter. Supporting cells, also known as neural glia, include astrocytes, oligodendrocytes and microglia; they form the white matter. They provide nutrition, digest the debris of neurons, form myelin sheath to increase neuronal communication speed, and support the architectures of neurons.

1.2.1 Structural changes

Normal aging associated changes on cerebral cortex include cortical shrinkage, neuronal loss, dendrites loss and synaptic changes [Salat et al, 2005; Peters 2002]. They will alter cortex structure and neurochemistry. These alternations will affect old adults' cognitive functions and behavioral performances. Shrinkage of human cerebral cortex, which accompanies by brain weight loss and enlarged ventricular volume have been reported by magnetic resonance imaging studies in old persons.

The major cause of shrinkage is loss of white matter in cerebral cortex [Ferro et al, 2002]. The functional decline related to white matter loss is axon demyelination and speed reduction of bioelectrical (neural) signal transmission. Though neuronal loss (gray matter) is also present as age increases, it is unknown whether neural loss leads to significant structural changes and it is unlikely to be the major cause of functional decline in normal aging [Peters 2002].

Dendrites are critical structures to form synaptic connections for inter neuron information transmissions [Peinado 1998]. Significant age associated dendrite loss on cerebral cortex has been reported in old persons and it includes dendrites shortening, decreased dendrite branches and loss of dendrite spines of pyramidal neurons [Kril 2003]. The dendrite loss may limit the activities of postsynaptic substrate in aged human brains and limit speed and accuracy of interneuron communications [Peters 2002].

Synapse is the specified junction between neurons for interneuron communication. Regional specified loss of synapses is present in aged animal and human brains. Changes in synaptic connections and the ability to form new synapses (also known as plasticity) also have been found. The ability to form new synapses is the basis of learning and memory. Plasticity is maintained throughout lifetime, however, as age increases, this ability will decline [Kril 2003].

1.2.2 Neurochemical changes

Age associated neurochemical changes in central nervous system include the reduction or increment of certain neurotransmitter synthesis. For instance, acetylcholine is one of the major neurotransmitters in cerebral cortex and it plays a key role in modulating auditory attention and working memory [Casu 2002]. Blocking cholinergic system functions by injecting a cholinergic antagonist to healthy subjects affects the regulation of auditory working memory and novelty stimuli detection [Levin 2002].

Inefficiency or breakdown in cholinergic systems in aged animal models and old human subjects have been reported and these changes are associated with declined behavioral performance in attention and working memory tasks [Tsukada et al., 2004]. Another major neurotransmitter system, the dopaminergic (DA) pathways in human cerebral cortex, is considered to be involved in executive functions, visuospatial skill, episodic memory, verbal fluency, perceptual speed and reasoning. Decline of DA functions is correlated positively with impairment in motor performances and cognitive functions of aged human subjects [Bäckman et al., 2005].

1.3 Brief review of auditory information processing

Auditory system converts sound from physical energy to neural signals and allows meaningful perception via signal processing in peripheral and central auditory pathways. This procedure includes following steps. Sound waves first pass through the outer ear; and it's transduced in the middle ear to a suitable range of pressure changes and converted to neural signals in inner ear via cochlea. Cochlea is filled with cochlear fluid and is tightly coiled as a spiral-like structure. Upper half of the cochlea is called the scala vestibuli and the lower part is called scala tympani. These two parts are separated by a cochlear partition. The cochlear partition contains basilar membrane and organ of Corti. Organ of Corti lies on top of the basilar membrane and below the tectorial membrane and it contains auditory receptors known as hair cells. Hair cells convert mechanical energy into neural signals through the vibration of its fine cilia. When sound waves enter the inner ear, cochlear fluid will vibrate, which leads to the vibration of cilia. Vibrations of the cilia generate electrical impulses, and then the electrical signals lead to release of chemical transmitters that generates action potentials in neural fibers.

After sounds are transduced into electrical signals, auditory nerves carry the signals first to the cochlear nucleus, second to the signal synapses in the superior olivary nucleus in the brain stem, next to the inferior colliculus of the midbrain and then to the medial geniculate nucleus of the thalamus (MGN). From MGN, the nerve fibers go to the primary auditory cortex (PAC) in the temporal lobe.

Auditory pathways are bilaterally organized and sound input can be either ipsi- or contralateral and most of the afferent nerve fibers project to the contralateral auditory cortex. Auditory cortex (AC) is the temporal region of cerebral cortex that contains neural circuits responsive to auditory stimuli. It receives afferent input from the medial geniculate nucleus (MGN) of the thalamus. Auditory input is first received in the core areas (the primary auditory cortex), including AC and some nearby areas [Brugge, 1985] and are then sent to areas surrounding the core, called the secondary auditory cortex, and then to the auditory association cortex for further analysis [Binder et al., 1994; Poremba et al., 2003] (see Figure 1.2).

1.4 Normal aging associated changes in auditory sensory processing

Normal aging associated changes can occur in both peripheral and central auditory pathways and these changes can be measured at different functional levels and with different time scales via psycho-physiological methods. For instance, in peripheral auditory system, electrocochleogram is measured with an electrode near the round window in the inner ear [Bohorquez et al., 2005]. These responses are very early, having latencies of 1~4 ms. Brainstem auditory evoked potentials are a set of seven positive waves during the first 12 ms following sound onset [Papathanasiou et al., 2005].

Aging associated neural changes in PAS and CAS may occur independently. Old adults with normal hearing threshold (normal hearing threshold is an indication of a well functioning peripheral auditory system) still may experience hearing difficulties attributed to aging associated changes in CAS.

Middle latency evoked potential/magnetic fields are the activations in CAS occurring around 50 ms after auditory stimulus onset. It is referred as M50 when measured with MEG. M50 most likely originates in primary auditory cortex near Heschl's gyrus [Hanlon et al., 2005]. The functional correlates of M50 are uncertain, but it is clearly associated with initial stimulus registration and can be modulated by attention [Chait et al., 2004]. Besides, source strength and latency of M50 change as age increases, with old subjects showing stronger source strength than young subjects [Pekkonen et al., 2005].

Evoked response in the CAS occurring near 100ms after stimuli onset is referred as M100. M100 may have multiple sources depending on features of the auditory stimulus and task requirements [Chait et al., 2004]; the locations of its sources include Heschl's gyrus, but a primary origin of this component is in the planum temporale [Ackermann et al., 2001]. The strength and latency of M100 are sensitive measurements of aging associated changes, for instance, M100 and N1 (the electroencephalograph analog of M100) strength is larger among old subjects than young subjects [Pekkonen et al., 2005; Smith et al, 1980], and strength of M100 is typically larger in right than in left hemisphere for nonverbal stimuli in normal young adults, but the same pattern has been less frequently reported for old individuals [Hertrich et al., 2004]. Moreover, old subjects' N1 amplitude is more sensitive to stimulus intensity increasing [Laffont et al., 1989] and the N1 latency decreases in old adults [McArthur et al., 2002].

Another evoked response in CAS is M200, occurring near 200 ms after the onset of auditory stimuli. M200 is sensitive to physical parameters of stimuli and it is also affected by participants' attention [Gilmore et al., 2005]. When measured with EEG, P200's amplitude (the electroencephalograph analog of M200) is stronger in young adults than old adults but no latency differences are found between age groups [Anderer et al., 1996].

1.5 Normal aging associated changes in auditory working memory

Baddeley proposed an important working memory model. The model hypothesized specialized storage systems for verbal or phonological information (phonological loop) and visuospatial (visuospatial sketchpad) information. The two storage systems are functionally separate. A central executive process is in charge of using the information stored in phonological loop and visuospatial sketchpad to perform complex cognitive tasks [Reuter-Lorenz et al., 2005].

In an experimental context, working memory refers to the limited cognitive capacity to hold and manipulate ongoing contextual information in mind for several seconds and it is the result of human ability to control attention and sustain its focus on a particular active mental representation when facing the environmental/external or internal distractors [Reuter-Lorenz et al., 2005]. The ability associated with working memory is critically important in comprehension, reasoning, planning and learning; it has been reported widely that working memory is positively associated with performance level in cognitive tasks [Reuter-Lorenz et al., 2005]. Working memory has been well addressed in behavioral, neuron imaging and psycho-physiological studies; for instance, the studies of M300.

The auditory M300 complex is scalp recorded cognitive neuro-electro-magneto activities generated in an auditory oddball paradigm. In this paradigm, two types of auditory stimuli of unequal probability are presented. M300 will be recorded, when subjects' attention is driven to the infrequent auditory stimuli (known as target stimuli). Specifically, P300 (the electroencephalograph analog of M300) is the brain activation evoked by voluntary detection of the target auditory stimuli [Soltani et al., 2000]. The most recognized theory on M300's cognitive functions suggests that M300 is associated with activity updating in corticolimbic circuits during attention and working memory. M300 is considered as an assessment of central nervous system's ability to process new information and update working memory when attention is engaged in other tasks. The M300 amplitude is associated with attention resource allocation in working memory updating, the stronger the amplitude, the more resources are required. M300 latency is correlated negatively with mental function in normal subjects and shorter latency is related to superior cognitive performance [Soltani et al., 2000].

M300's source distribution is critical to understand its association with cognitive functions. Psychophysical studies indicate that hippocampus is not M300's prominent generator; the activity of outer layers of the brain, such as cortex, dominates the measured M300 signal [Trahms et al., 1993]. It suggested that P300 might be generated from mesial temporal structures [Soltani et al., 2000], supramarginal gyrus (Brodmann area 40), inferior frontal gyrus (Brodmann area 45), middle frontal gyrus (Brodmann area 46) [Wang et al., 2001] and dorsal lateral prefrontal areas [Anderer et al., 2003]. Besides, damage on temporo-parietal junction, including the posterior temporal plane and superior temporal sulcus, will result in severe reduction of P300 activity at posterior scalp sites in the auditory oddball paradigm [Soltani et al., 2000].

Normal aging associated differences of M300 correlate closely with the fact that the ability to selectively attend to auditory stimuli and manipulate information in working memory is changed as individual ages. For example, old adults have more difficulty than young adults in detecting infrequent auditory targets embedded in a sequence of distractors [Alain et al., 1996; Karayanidis et al., 1995]. M300's magnitude, latency and source distribution are affected significantly by subjects' age. M300's amplitude and latency decreases and increases respectively as the progress of normal aging [Friedman et al., 1997]. M300's source distribution moves forward from temporal-parietal association to frontal as subjects age increase. M300 recorded from young subjects demonstrates a parietal source distribution to the target auditory stimuli in oddball paradigm; while M300 recorded from old subjects shows a frontal and posterior source distribution. The different source distributions have been interpreted as age-associated changes in the efficiency of frontal lobe functioning [Friedman et al., 1997; Anderer et al., 1996; 1998].

1.6 Hypotheses in present study

Sensory processing is the gateway to interact with the external environment. The quality of this processing, i.e. how well the sensory information is analyzed by the macroscopic neural groups, will directly affect higher-level cognitive functions, such as attention, memory and learning. It is a well-known fact that ability to process sensory information is compromised along with normal aging and these changes are associated with alternations in cognitive functions, such as attention and working memory.

In present thesis, old and young subjects without physical or mental deficits were recruited for data recording. An auditory oddball paradigm was used to assess normal aging associated changes in: 1) sensory processing and 2) working memory using MEG measurement. The former is investigated by analyzing source latency, strength and distributions of M50, M100 and M200 responses. The latter is investigated by analyzing sources latency, strength and distributions of M300.

It is hypothesized that: 1) normal aging associated macroscopic neural changes comprise old subjects' ability to process auditory sensory information; this will be shown as age associated differences on source latency, strength and scalp distribution of auditory evoked responses (M50, M100 and M200); 2) working memory ability is also undergone normal aging associated changes; this will be shown as age associated activation difference of M300 (latency, source strength and distribution).

2 Methods

2.1 Participants

Twenty-seven right-handed volunteers participated in present study. Fifteen young subjects (age ranges from 18 to 22 years old, M=19.3, SD=1.4) were undergraduate students recruited from the Human Subjects Research Pool in Department of Psychology at the University of Georgia. They received course credits as compensation for participation. Twelve old subjects (age ranges from 65 to 86, M=72.4, SD=6.2) were recruited from the local community. They received monetary compensation for participation.

A standard telephone interview was used for all subjects to exclude individuals with evidence of neurological hard signs, history of head trauma, potentially confounding treatments, current psychoactive substance use, a major psychiatric disorder, other medical conditions that could complicate interpretation of MEG data. The telephone interview was followed by an evaluation in the laboratory to verify the telephone interview information.

Participants were mentally and physically healthy, and indeed were all functioning at a high level with Global Assessment of Functioning (Axis 5 of the DSM-IV) (American Psychiatric Association et al. 1994) scores between 81 and 100 for all subjects. In addition, all subjects were administered the information subscale of the WAIS-R, and the groups did not differ significantly on their age-adjusted subtest scores (young subjects M=12, SD=2; old subjects M=13.3, SD=1.5).

This study was approved by the Institutional Review Board at the University of Georgia; all subjects provided informed consent prior to participation.

After subjects completed consent forms and questionnaires, binaural hearing thresholds were determined using the method of limits with 1 KHz tones generated by an auditory stimulator (Grass Model 10H2S audiometric headphones and Grass Model S10CTCM auditory stimulator). All subjects had hearing thresholds within normal limits, although young individuals had lower thresholds (M threshold= 10.2 dB HL, SD=4.4) than old individuals (M threshold=17.1 dB HL, SD=11.1).

2.2 Subject preparation and experimental setup

All subjects were asked to change into medical scrubs before being seated in the MEG recording environment (inside an IMEDCO shielded room). Subjects were prepared for recording by attaching three head localization coils (located at nasion, left and right preauricular points), and Ag-AgCl electrodes for recording horizontal (an electrode located at the outer canthus of each eye) and vertical (electrodes above and below the left eye) eye movements, in addition to a forehead ground. Subjects were seated in a comfortable, pneumatically controlled chair. If the subject's head did not fit snugly in the dewar, an inflatable air bladder was fitted to the subject's head to help provide head stabilization throughout testing. Fitted inserts were placed in each ear, to which were attached echo-free plastic tubing for delivery of auditory stimuli (nearly linear frequency response between 500 and 4000 Hz).

2.3 Stimuli and tasks

Auditory stimuli were generated by Presentation (Version 9.0, Neurobehavioral Systems, Inc., Albany, CA). Two pure tones were used: a 1200Hz pure tone was presented with lower probability as 'target stimuli'; a 1000Hz pure tone was presented with higher probability as

'standard stimuli'. There were 864 total trials in the experiment with 144 trials of 1200Hz tone and 720 trials of 1000Hz tone. The 864 trials were presented in 4 blocks with one second ISI. There are 216 trials in each block (36 target stimuli and 180 standard stimuli) and the 180 standard stimuli are classified into three categories by their repetition rate, with 96 stimuli of low repetition rate, 60 stimuli of middle repetition rate and 24 stimuli of high repetition rate. The trials were randomly presented to the subjects and there were no target stimuli presented next to each other.

A rear projection screen was placed approximately 80 cm in front of the subject displaying a dim white cross on which subjects were asked to fixate throughout testing. Sample stimuli were provided to ensure that subjects understood the nature of the task. Subjects were instructed to pay attention to auditory stimuli presented to both ears and silently count the number of target stimuli whenever it occurred. Subjects were asked to report the number of target stimuli they counted after the experiment.

2.4 MEG recording

MEG recordings were obtained using a 143-channel CTF OMEGA whole-head system (VSM MedTech, Canada). Data were recorded continuously at 600 Hz sampling frequency with an analogue filter bandpass of 1-250 Hz. Heads' position relative to MEG sensor locations was measured at the beginning and end of testing. For this standard procedure, small currents were introduced through the frequency-specific coils affixed to the fiducial points, and the locations of these coils were determined by fitting equivalent current dipoles to the generated magnetic fields. This procedure allowed us confirmation that the subjects' heads were in the same position at the start and end of testing. No subject used in this study moved more than 1.5 mm in any plane.

2.5 MEG data preprocessing

MEG data were screened and segmented around stimulus triggers using BESA (Version 5.0, MEGIS Software GmbH, Germany). Trials were automatically eliminated if they contained MEG signals larger than 2.5 pT, had blinks and/or other movement artifacts. Two groups did not differ on the number of usable trials (young standard trials M=411.7, SD=67.2, old standard trials M=366.9, SD=52.7, p=.07; young target trials M=85.3, SD=18.6, old target trials M=74.9, SD=17.6, p=.15) nor on the number of correct responses, p=.12 (old subject, mean=138.6, S.D.=4.1; young subjects mean=140.9, S.D.=3.2).. Data were digitally band-pass filtered from 1-30 Hz (-6 dB for each edge).

2.6 Response latency

Auditory brain responses, M50, M100 and M200 evoked by standard stimuli and target stimuli as well as M300 evoked by target stimuli were analyzed. First, time points at which each evoked response reached its maximum magnitude were identified based on the global field power (GFP) of the grand averaged data (see Figure 2.1-A for standard stimuli and Figure 2.1-B for target stimuli).

Second, time windows around the maximum magnitude of each evoked response were quantified. For early response (M50 and M100), a 16.7 ms time window with the time point of maximum source magnitude at the center was defined. For late response (M200 and M300), a 33.3 ms time window with the time point of maximum source magnitude at the center was defined (see Table 1).

2.7 Source localization

Source reconstructions of each evoked response were performed with BESA. L2 minimum norm algorithm was used to localize sources. A spherical single shell model (with the diameter equal to the distance between the left and right pre-auricular points for each subject) was used to model the head for all source analyses. The source distribution is specified *a priori* and in present case, 162 sources were equally spaced across the spherical head shell surface. The final solution was obtained using the signal subspace to calculate the correlation to the lead field of each source, and depth weighting to ensure that both deep and superficial sources generated a similarly focal solution in source space. Noise estimates came from the 15% lowest sample vectors, averaged over channels. Source strength was quantified by averaging L2 minimum norm values within the time windows defined for each evoked responses (with MATLAB version 6.0).

3 Results

3.1 Standard stimuli evoked responses

Response latency and source strength of standard stimuli evoked auditory brain responses, including M50, M100 and M200, were analyzed by fitting general linear models in SAS (Version 8.0, SAS Institute Inc. Cary, NC).

For brain responses' latency, general linear models were fitted with 'age' (old and young subjects) and 'repetition rate' (low, middle and high) as independent variables; response latency as dependent variable. Variances from individual subjects were used as error term to estimate significant level of statistical test.

For brain responses' source strength, general linear models were fitted in SAS source by source (162 sources in total) to localize cortical areas of significant differences with 'age' and 'repetition rate' as independent variables; source strength as dependent variable. To maintain family-wise alpha at .05, the following criterions was met: at least three neighboring sources sharing sides in space are statistically significant at the same time. Variances from individual subjects were used as error term to estimate significant level of statistical test.

3.1.1 Latency and source strength of M50

No significant effects of age, $F(1,25)=.88$, $p=.36$, or stimulus rate, $F(2,50)=.21$, $p=.82$, are found for M50's source latency.

For strength, sources of significant strength difference between age groups (Fs' $(1,25) \geq 8.21$, $p \leq .01$) are localized at right auditory cortex (Brodmann areas 41 and 42), with old subjects showing stronger source strength than young subjects (see Figure 3.1-A).

Sources with significant stimulus rate effects (Fs' (2,50) ≥ 4.82, p ≤ .01) are localized at posterior parietal cortex (Brodmann area 7), bilateral frontal cortex (Brodmann areas 9 and 46). Multiple comparisons indicate that source strength of stimuli with low repetition rate is stronger than middle and high repetition rate, ps' < .02; while no differences are found between middle and high repetition rate, see Figure 3.2.

3.1.2 Latency and source strength of M100

For source latency, main effect of age is significant, F (1,25)=6.11, p=.02, with young subjects (M=115.21 ms, SD=11.01) taking longer than old subjects (M=108.98 ms, SD=5.14) to reach maximum source strength. No significant stimulus rate effects are found, F(2,50)=.16, p=.85. For strength, sources with significant difference between age groups (Fs' (1,25) ≥ 5.14, p ≤ .03) are localized at bilateral auditory cortex (Brodmann areas 41 and 42); with old subjects showing stronger source strength than young subjects, see Figure 3.1-A.

Sources of significant stimuli rate effects (Fs' (2,50) ≥ 3.94, p≤ .03) among standard stimuli's sequences are localized at right supramarginal gyrus (Brodmann area 40). Multiple comparisons indicate that source strength of stimuli with low repetition rate is stronger than middle and high repetition rate, ps' < .03, while no differences are found between middle and high repetition rate, see Figure 3.2.

3.1.3 Latency and source strength of M200

No significant age effects, F(1,25)=.15, p=.70, or stimulus rate effects, F(2,50)=1.61, p=.21, are found for M200's source latency. For strength, sources of significant strength difference between age groups (Fs' (1,25) ≥ 5.06, p≤ .03) are localized at bilateral auditory cortex (Brodmann areas 41 and 42); with old subjects showing stronger source strength than young subjects, see Figure 3.1-A. No significant stimulus rate effects are found.

3.2 Target stimuli evoked responses

Response latency and source strength of target stimuli evoked auditory brain responses, including M50, M100, M200 and M300, were analyzed by fitting general linear models in SAS (Version 8.0, SAS Institute Inc. Cary, NC).

For brain responses' latency, general linear models were fitted with 'age' (old and young subjects) as independent variable; response latency as dependent variable. Variances from individual subjects were used as error term to estimate significant level of the statistical test.

For brain responses' strength, general linear models were fitted in SAS source by source (162 sources in total) to localize cortical areas of significant differences with 'age' as independent variable; source strength as dependent variable. To maintain family-wise alpha at .05, the following criterions was met: at least three neighboring sources sharing sides in space are statistically significant at the same time. Variances from individual subjects were used as error term to estimate significant level of the test.

3.2.1 Latency and source strength of M50

No effects are found for latency, $F(1,25)=.92$, $p=.35$. For strength, sources of significant difference between age groups (Fs' $(1,25) \geq 5.63$, $p \leq .03$) are localized at bilateral auditory cortex (Brodmann areas 41 and 42); with old subjects showing stronger source strength than young subjects, see Figure 3.1-B.

3.2.2 Latency and source strength of M100

For source latency, main effect of age is significant, $F(1,25)=18.16$, $p < .001$, with young subjects ($M=127.14$ ms, $SD=14.89$) taking longer than old subjects ($M=107.92$ ms, $SD=5.73$) to reach maximum source strength.

For source strength, sources of significant strength difference between age groups (Fs' (1,25)≥ 7.89, p ≤ .01) are localized at bilateral auditory cortex (Brodmann areas 41 and 42); with old subjects showing stronger source strength than young subjects, see Figure 3.1-B.

3.2.3 Latency and source strength of M200

No effects are found for latency, F(1,25)=.46, p=.50. For strength, sources of significant strength difference between age groups (Fs' (1,25) ≥ 7.50, p ≤ .01) are localized at bilateral auditory cortex (Brodmann areas 41 and 42); with old subjects showing stronger source strength than young subjects, see Figure 3.1-B.

3.2.4 Latency and source strength of M300

For source latency, main effect of age is significant, F(1,25)=4.08, p=.05, with old subjects (M=293.33 ms, SD=35.06) taking longer than young subjects (M=268.20 ms, SD=29.65) to reach maximum source strength.

For strength, sources of significant strength difference between age groups (Fs' (1,25)≥ 9.45, p ≤ .01) are localized. Young subjects having stronger source strength at bilateral auditory cortex (Brodmann areas 41 and 42), right parietal areas (Brodmann areas 39), right inferior premotor cortex (Brodmann area 6) and right Brodmann area 44; while old subjects still have stronger source at medial frontal cortex (Brodmann areas 8 and 9), see Figure 3.3.

4 Discussions

4.1 Normal aging associated changes

The present thesis replicated and extended previous research on normal aging associated brain evoked responses in non-verbal auditory information processing. The experiment task is well instructed and understood by both age groups, besides; the old subjects recruited for data recording are all highly functioning. Although no significant behavioral performance differences have been found, the auditory brain evoked responses do bear major deviation between age groups.

4.1.1 Auditory sensory processing

For both age groups, standard and target stimuli evoked M50, M100 and M200 responses are localized around bilateral auditory cortex (Brodmann areas 41 and 42) (see Figure 3.1). Old subjects' M100 latency (evoked by both standard and target stimuli) is significantly faster than young subjects'. Besides, old subjects show stronger source strength than young subjects on M50, M100 and M200 responses evoked by both standard and target auditory stimuli.

Due to the fact that the old subjects participated in present study do not have neurological pathology difficulties; it is reasonable that the early brain responses associated with auditory sensory processing (M50 and M100) have the same source distributions on bilateral auditory cortex. This result is consistent with a recent study [Gao et al, 2005] that there are no significant age differences regarding the sources localization of auditory evoked responses. The results that old subjects show stronger source activations of M50, M100 are in line with similar studies.

M50 is considered to be the early stage of sensory stimuli processing. It has been reported that M50's amplitude is larger in old subjects, a phenomenon attributed to age-associated

function alternation of inhibitory neural structures related to the M50's neural generators [Pekkonen et al, 2005]. Old subjects showing enlarged M50 source activations may develop an age-associated alternation on efficiently inhibiting sensory stimulus. M100 is considered an index of early sensory attention gating processes [Hillyard et al, 1973]. In similar EEG studies, it is reported that old subjects have larger N1 (M100's counterpart when recorded with EEG) amplitude than young subjects [Chao et al, 1997] and the enlarger N1 amplitude is an indication of compromised attention gating in old subjects [Chao et al, 1997]. The similar pattern is also found in present study along with shortened brain response latency in old subjects. In aged animal model studies, there are significant age-related decreases of the inhibitive neurotransmitters GABA in primary auditory cortex [Ling et al., 2005]. This age-associated alternation in inhibition regulation could contribute to functional changes in auditory cortex and yield over activations.

M200's sources are also stronger for old subjects though no latency differences are found. M200 sources evoked by standard stimuli are localized at bilateral auditory cortex (Brodmann areas 41 and 42) for both age groups; while young subjects' M200 sources evoked by target stimuli are extended into bilateral supramarginal gyrus (Brodmann area 40), which is associated with attentional modulation [Rosano et al., 2005], and old subjects' M200 sources remain at bilateral auditory cortex (Brodmann areas 41 and 42). M200 is theorized to index stimulus evaluation, encoding, decision-making and stimulus comparison operations [Gilmore et al, 2005]. Different M200 source distribution between old and young may be the evidence of age-associated changes in stimuli evaluation and attentional modulation toward the target stimuli.

4.1.2 Auditory working memory

M300 is the brain activation evoked by target stimuli. Young subjects show stronger activations on M300 source in certain cortical areas (see Figure 3.3), including bilateral auditory cortex (Brodmann areas 41 and 42), right parietal areas (Brodmann areas 39), right inferior premotor cortex (Brodmann area 6) and right Brodmann area 44, though old subjects have stronger source at medial frontal cortex (Brodmann areas 8 and 9). Further more, young subjects' neural reaction time on M300 is faster than old subjects.

The response magnitude and latency of M300 is considered as index of processing efficiency; the larger responses and faster occurrence of P300 (the electroencephalograph analog of M300) are associated with higher functions of central nervous system's ability in working memory updating and attention modulation [Soltani et al, 2000]. Age associated topographical alternation of M300 has been frequently reported. In line with current findings, young subjects' M300 are localized at bilateral temporal-parietal associations while old subjects' M300 sources are distributed toward the frontal areas [Friedman et al., 1997; Anderer et al., 1996; 1998]. Furthermore, young subjects' M300 latency is significantly shorter than old subjects. Findings from current study indicate that old subjects may have inefficient working memory processing.

The age associated response magnitude increments in present study is considered due to the fact that old individual's brain responses differently from young participants [Reuter-Lorenz 2005] and is consistent with previous studies. In a PET study, old and young adults' brain activations were compared while they were engaged in face or location matching tasks. Old subjects performed slower but with the equivalent accuracy levels as young subjects and their parietal and temporal areas were activated for both faces and location tasks; while the young subjects activated temporal areas for face tasks and parietal areas for locations [Grady et al.,

1992]. Other spatial and verbal working memory studies reported that old subjects activated more brain regions than young subjects when they were performing in the same tasks [Reuter-Lorenz et al., 2000]. The over-activation patterns observed in present study and other functional MRI studies may indicate a compensatory mechanism of old subjects. It has to be noticed that this over-activations occurs when old subjects have the same behavioral performances as young subjects. It can be argued then that old subjects have to use different strategies and recruit more brain regions as a supportive compensation to accomplish the task [Grady et al., 1994; Cabeza et al., 1997].

4.2 Stimulus rate effects

Significant stimulus rate effects are found on standard stimuli evoked M50 and M100 from both age groups. The response magnitude (M50 and M100's source strength) decreases as a function of standard stimulus repetition rate and this is in line with the reported findings that increased stimuli repetition rate is associated with decreased activation of relevant brain systems [Stephenson et al., 2003].

For M50, the activated brain areas associated with stimulus rate effects include left posterior parietal cortex (Brodmann area 7), bilateral frontal cortex (Brodmann area 9 and 46); for M100 the activated area is localized at right supramarginal gyrus (Brodmann area 40) [Kandel et al., 2000] (see Figure 7). These cortical areas are associated with task related attention reorientation (Brodmann areas 7 and 40) [Rosano et al., 2005]; memory retrieval and inhibition (Brodmann areas 46) [Nielson et al., 2002]; working memory, sustained attention and problem solving (Brodmann area 9) [Staffen et al, 2002]. The decreased activities in these areas may be associated with habituation to stimulus repetition [Budd et al, 1998] or a reduction in amplitude

of an evoked brain response with increasing stimulus frequency, known as rate effect. Rate effect is significantly associated with expectancy and it can affect the early-evoked brain response P50 (the electroencephalograph analog of M50) [Clementz et al, 2002]. However, no age-associated differences are found regarding the stimulus rate effects; both age groups have shown the same areas of activations though old subjects have stronger activations. This may be an indication that old subjects remain the ability to orient and control attention allocation, but they have to activate more brain regions to compensate.

4.3 Conclusions

Normal aging associated macroscopic neural changes do occur in central auditory system. Generally, old participants' brain responses have larger magnitude and faster speed than young participants in sensory information processing. This over-activation pattern in auditory cortex could be attributed to lack of inhibition in sensory processing. However, both age groups activate the same brain regions associated with stimulus rate discrimination, though old subjects have stronger response magnitude. These brain regions are considered to be involved in higher cognitive functions, such as attention reallocation, working memory and problem solving. For late brain responses associated with working memory, two age groups activate different cortical regions and old participants' response slower than young subjects. The different activation patterns could be attributed to compensation. In summary, findings in present thesis indicate that normal aging associated brain activation differences exist in the form of over-activation. At the sensory processing level, old participants' brain over-activation is associated with lack of inhibition to sensory input. As the brain activation evolves, this sensory processing related over-activation affect higher cognitive functions, such as working memory and attention reallocation.

REFERENCES

Ackermann, H., Hertrich, I., Mathiak, K., & Lutzenberger, W. (2001). Contralaterality of cortical auditory processing at the level of the M50/M100 complex and the mismatch field: a whole-head magnetoencephalography study. Neuroreport, 12(8), 1683-1687.

Alain, C., Ogawa, K. H., & Woods, D. L. (1996). Aging and the segregation of auditory stimulus sequences. J Gerontol B Psychol Sci Soc Sci, 51(2), 91-93.

Anderer, P., Pascual-Marqui, R. D., Semlitsch, H. V., & Saletu, B. (1998). Differential effects of normal aging on sources of standard N1, target N1 and target P300 auditory event-related brain potentials revealed by low resolution electromagnetic tomography (LORETA). Electroencephalogr Clin Neurophysiol, 108(2), 160-174.

Anderer, P., Semlitsch, H. V., & Saletu, B. (1996). Multichannel auditory event-related brain potentials: effects of normal aging on the scalp distribution of N1, P2, N2 and P300 latencies and amplitudes. Electroencephalogr Clin Neurophysiol, 99(5), 458-472.

Bäckman, L. & Farde, L., The role of dopamine systems in cognitive aging (2005). Cognitive neuroscience of aging : linking cognitive and cerebral aging. Oxford ; New York: Oxford University Press., 85-106.

Binder, J. R., Rao, S. M., Hammeke, T. A., Yetkin, F. Z., Jesmanowicz, A., Bandettini, P. A., et al. (1994). Functional magnetic resonance imaging of human auditory cortex. Ann Neurol, 35(6), 662-672.

Bohorquez, J., Ozdamar, O., Morawski, K., Telischi, F. F., Delgado, R. E., & Yavuz, E. (2005). Neuromonitoring of cochlea and auditory nerve with multiple extracted parameters during induced hypoxia and nerve manipulation. J Neural Eng, 2(2), 1-10.

Brugge, J. F. (1985). Patterns of organization in auditory cortex. J Acoust Soc Am, 78(1 Pt 2), 353-359.

Budd, T. W., Barry, R. J., Gordon, E., Rennie, C., & Michie, P. T. (1998). Decrement of the N1 auditory event-related potential with stimulus repetition: habituation vs. refractoriness. Int J Psychophysiol, 31(1), 51-68.

Cabeza, R., Grady, C. L., Nyberg, L., McIntosh, A. R., Tulving, E., Kapur, S., et al. (1997). Age-related differences in neural activity during memory encoding and retrieval: a positron emission tomography study. J Neurosci, 17(1), 391-400.

Cabeza, R., Nyberg, L., & Park, D. C. (2005). Cognitive neuroscience of aging : linking cognitive and cerebral aging. Oxford ; New York: Oxford University Press.

Casu, M. A., Wong, T. P., De Koninck, Y., Ribeiro-da-Silva, A., & Cuello, A. C. (2002). Aging causes a preferential loss of cholinergic innervation of characterized neocortical pyramidal neurons. Cereb Cortex, 12(3), 329-337.

Chait, M., Simon, J. Z., & Poeppel, D. (2004). Auditory M50 and M100 responses to broadband noise: functional implications. Neuroreport, 15(16), 2455-2458.

Chao, L. L., & Knight, R. T. (1997). Age-related prefrontal alterations during auditory memory. Neurobiology of Aging, 18(1), 87-95.

Clementz, B. A., Barber, S. K., & Dzau, J. R. (2002). Knowledge of stimulus repetition affects the magnitude and spatial distribution of low-frequency event-related brain potentials. Audiol Neurootol, 7(5), 303-314.

Ferro, J. M., & Madureira, S. (2002). Age-related white matter changes and cognitive impairment. J Neurol Sci, 203-204, 221-225.

Friedman, D., Kazmerski, V., & Fabiani, M. (1997). An overview of age-related changes in the scalp distribution of P3b. Electroencephalogr Clin Neurophysiol, 104(6), 498-513.

Gençer N.G., Acar C.E. & Tanzer I.O., Foreard proglem solution of magnetic source imaging (2003). Magnetic source imaging of the human brain. Mahwah, N.J.: Lawrence Erlbaum., 77-100

Gilmore, C. S., Clementz, B. A., & Buckley, P. F. (2005). Stimulus sequence affects schizophrenia-normal differences in event processing during an auditory oddball task. Brain Res Cogn Brain Res, 24(2), 215-227.

Grady, C. L., Maisog, J. M., Horwitz, B., Ungerleider, L. G., Mentis, M. J., Salerno, J. A., et al. (1994). Age-related changes in cortical blood flow activation during visual processing of faces and location. J Neurosci, 14(3 Pt 2), 1450-1462.

Grandori, F., Hoke, M., & Romani, G. L. (1990). Auditory evoked magnetic fields and electric potentials. Basel ; New York: Karger.

Hanlon, F. M., Miller, G. A., Thoma, R. J., Irwin, J., Jones, A., Moses, S. N., et al. (2005). Distinct M50 and M100 auditory gating deficits in schizophrenia. Psychophysiology, 42(4), 417-427.

Hertrich, I., Mathiak, K., Lutzenberger, W., & Ackermann, H. (2004). Time course and hemispheric lateralization effects of complex pitch processing: evoked magnetic fields in response to rippled noise stimuli. Neuropsychologia, 42(13), 1814-1826.

Hillyard, S. A., Hink, R. F., Schwent, V. L., & Picton, T. W. (1973). Electrical signs of selective attention in the human brain. Science, 182(108), 177-180.

Jerger J, L. H. (2004). Priciples and clinical applications of auditory evoked potentials in the geriatric population. Phys Med Rehabil Clin N Am., 15(1), 235-250.

Kandel, E. R., Schwartz, J. H., & Jessell, T. M. (2000). Principles of neural science (4th ed.). New York: McGraw-Hill, Health Professions Division., 328-329.

Karayanidis, F., Andrews, S., Ward, P. B., & Michie, P. T. (1995). ERP indices of auditory selective attention in aging and Parkinson's disease. Psychophysiology, 32(4), 335-350.

Kaufman L., & Lu Z.-L., Basics of neuromagnetism and magnetic source imaging (2003). Magnetic source imaging of the human brain. Mahwah, N.J.: Lawrence Erlbaum., 1-42

Kril, J.J., Structural changes in the aging human brain (2003). The ageing brain: the neurobiology and neuropsychiatry of ageing. Lisse ; Exton (PA): Swets & Zeitlinger Publishers. 35-48.

Levin, E. D. (2002). Nicotinic receptor subtypes and cognitive function. J Neurobiol, 53(4), 633-640.

Lewine, J. D., & Orrison, W. W., Jr. (1995). Magnetic source imaging: basic principles and applications in neuroradiology. Acad Radiol, 2(5), 436-440.

Ling, L. L., Hughes, L. F., & Caspary, D. M. (2005). Age-related loss of the GABA synthetic enzyme glutamic acid decarboxylase in rat primary auditory cortex. Neuroscience, 132(4), 1103-1113.

Lord, S.R. & Georrge R.S., Neurophysiological, sensory and motor changes with ageing (2003). The ageing brain: the neurobiology and neuropsychiatry of ageing. Lisse ; Exton (PA): Swets & Zeitlinger Publishers. 63-74.

Lu, Z.-L., & Kaufman, L. (2003). Magnetic source imaging of the human brain. Mahwah, N.J.: Lawrence Erlbaum.

Nielson, K. A., Langenecker, S. A., & Garavan, H. (2002). Differences in the functional neuroanatomy of inhibitory control across the adult life span. Psychol Aging, 17(1), 56-71.

Okada Y., Toward understanding the physiological origins of neuromagnetic signals (2003). Magnetic source imaging of the human brain. Mahwah, N.J.: Lawrence Erlbaum., 43-76

Orrison, W. W. (1995). Functional brain imaging. St. Louis: Mosby.

Papathanasiou, E., Piperidou, C., Iliopoulos, I., Myrianthopoulou, P., Pilavakis, P., & Papacostas, S. (2005). Brainstem auditory evoked responses that disappear during sleep: a possible manifestation of a neurogenic vestibular evoked response. Electromyogr Clin Neurophysiol, 45(5), 263-266.

Peinado, M. A. (1998). Histology and histochemistry of the aging cerebral cortex: an overview. Microsc Res Tech, 43(1), 1-7.

Pekkonen, E., Jaaskelainen, I. P., Kaakkola, S., & Ahveninen, J. (2005). Cholinergic modulation of preattentive auditory processing in aging. Neuroimage, 27(2), 387-392.

Peters, A. (2002). The effects of normal aging on myelin and nerve fibers: a review. J Neurocytol, 31(8-9), 581-593.

Plonsey, R., & Barr, R. C. (1995). Electric field stimulation of excitable tissue. IEEE Trans Biomed Eng, 42(4), 329-336.

Poremba, A., Saunders, R. C., Crane, A. M., Cook, M., Sokoloff, L., & Mishkin, M. (2003). Functional mapping of the primate auditory system. Science, 299(5606), 568-572.

Reuter-Lorenz, P. A., Jonides, J., Smith, E. E., Hartley, A., Miller, A., Marshuetz, C., et al. (2000). Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. J Cogn Neurosci, 12(1), 174-187.

Reuter-Lorenz, P. A., & Lustig, C. (2005). Brain aging: reorganizing discoveries about the aging mind. Current Opioion in Neurobiology, 15, 245-251.

Rosano, C., Aizenstein, H., Cochran, J., Saxton, J., De Kosky, S., Newman, A. B., et al. (2005). Functional neuroimaging indicators of successful executive control in the oldest old. Neuroimage. (article in press).

Sachdev, P. (2003). The ageing brain: the neurobiology and neuropsychiatry of ageing. Lisse ; Exton (PA): Swets & Zeitlinger Publishers.

Scherg, M., Fundamentals of dipole source potentials analysis (1990). Auditory evoked magnetic fields and electric potentials. Basel; New York: Karger. 40-68.

Soltani, M., & Knight, R. T. (2000). Neural origins of the P300. Crit Rev Neurobiol, 14(3-4), 199-224.

Speckmann, E. J., Kohling, R., Lucke, A., Straub, H., Wittkowski, W., Elger, C. E., et al. (1998). Microcutting of living brain slices by a pulsed ultrafine water jet which allows simultaneous electrophysiological recordings (micromingotome). J Neurosci Methods, 82(1), 53-58.

Staffen, W., Mair, A., Zauner, H., Unterrainer, J., Niederhofer, H., Kutzelnigg, A., et al. (2002). Cognitive function and fMRI in patients with multiple sclerosis: evidence for compensatory cortical activation during an attention task. Brain, 125(Pt 6), 1275-1282.

Stephenson, C. M., Suckling, J., Dirckx, S. G., Ooi, C., McKenna, P. J., Bisbrown-Chippendale, R., et al. (2003). GABAergic inhibitory mechanisms for repetition-adaptivity in large-scale brain systems. Neuroimage, 19(4), 1578-1588.

Teale, P., Sheeder, J., Rojas, D. C., Walker, J., & Reite, M. (1998). Sequential source of the M100 exhibits inter-hemispheric asymmetry. Neuroreport, 9(11), 2647-2652.

Tsukada, H., Nishiyama, S., Fukumoto, D., Ohba, H., Sato, K., & Kakiuchi, T. (2004). Effects of acute acetylcholinesterase inhibition on the cerebral cholinergic neuronal system and cognitive function: Functional imaging of the conscious monkey brain using animal PET in combination with microdialysis. Synapse, 52(1), 1-10.

Uutela, K., Hamalainen, M., & Somersalo, E. (1999). Visualization of magnetoencephalographic data using minimum current estimates. Neuroimage, 10(2), 173-180.

Vrba, J., & Robinson, S. E. (2001). Signal processing in magnetoencephalography. Methods, 25(2), 249-271.

Walters, N. B., Egan, G. F., Kril, J. J., Kean, M., Waley, P., Jenkinson, M., et al. (2003). In vivo identification of human cortical areas using high-resolution MRI: an approach to cerebral structure-function correlation. Proc Natl Acad Sci U S A, 100(5), 2981-2986.

Wang Z.J. & Kaufamn L., Magnetic source imaging: search for inverse solutions (2003). Magnetic source imaging of the human brain. Mahwah, N.J.: Lawrence Erlbaum., 101-134

Williamson, S. J., & Kaufman, L. (1990). Evolution of neuromagnetic topographic mapping. Brain Topogr, 3(1), 113-127.

Table 1 Time windows for source activation (ms): Mean ± S.D.

	Stimuli		Older subjects							Young subjects						
M50	Standard	early	55.08	±	6.33	~	71.78	±	6.33	50.96	±	8.72	~	67.66	±	8.72
		middle	52.98	±	6.43	~	69.68	±	6.43	52.85	±	9.67	~	69.55	±	9.67
		late	53.65	±	5.72	~	70.35	±	5.72	50.52	±	10.38	~	67.22	±	10.38
	Target		55.44	±	5.51	~	72.14	±	5.51	58.51	±	9.94	~	75.21	±	9.94
M100	Standard	early	101.51	±	4.95	~	118.21	±	4.95	107.36	±	7.15	~	124.06	±	7.15
		middle	100.26	±	5.16	~	116.96	±	5.16	106.75	±	10.32	~	123.45	±	10.32
		late	100.12	±	5.62	~	116.82	±	5.62	106.48	±	14.94	~	123.18	±	14.94
	Target		99.57	±	5.13	~	116.27	±	5.13	118.79	±	14.89	~	135.49	±	14.89
M200	Standard	early	175.38	±	24.18	~	208.78	±	24.18	165.09	±	21.84	~	198.49	±	21.84
		middle	167.44	±	17.78	~	200.84	±	17.78	168.45	±	24.50	~	201.85	±	24.50
		late	174.97	±	23.16	~	208.37	±	23.16	175.22	±	26.17	~	208.62	±	26.17
	Target		183.86	±	18.97	~	217.26	±	18.97	189.35	±	22.18	~	222.75	±	22.18
M3b	Target		276.63	±	35.06	~	310.03	±	35.06	251.50	±	29.65	~	284.90	±	29.65

* The mid-point of each time window is the time point when source reaches the maximum strength

Figure 1.1 Magneto-encephalography (MEG): (a) the physics basis of MEG recording; (b) the neuronal electrical-magnetic fields that can be captured by MEG recording sensors.

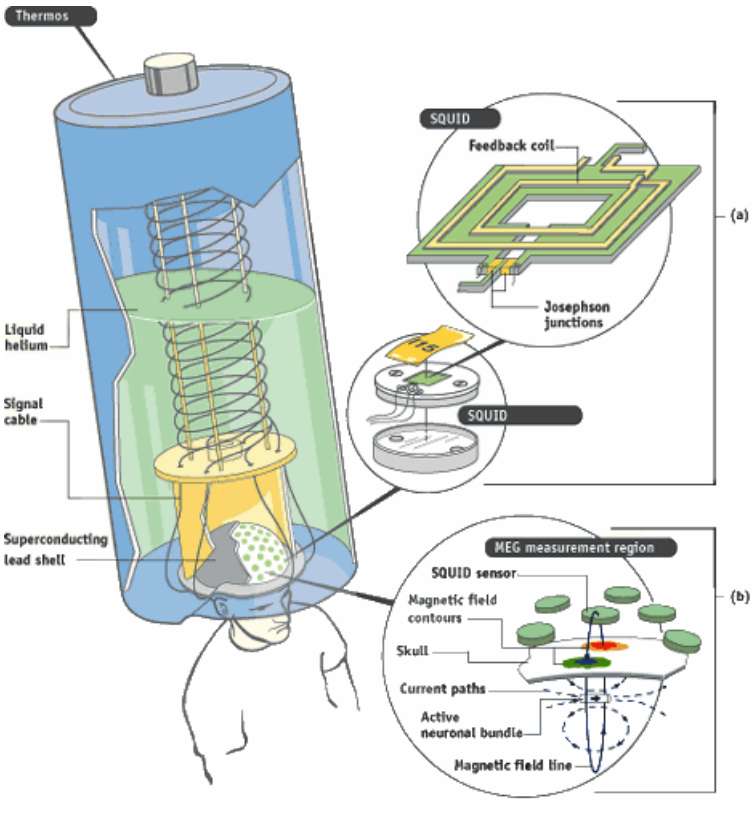

Thermos
Liquid helium
Signal cable
Superconducting lead shell
SQUID
Feedback coil
Josephson junctions
(a)
SQUID
MEG measurement region
SQUID sensor
Magnetic field contours
Skull
Current paths
Active neuronal bundle
Magnetic field line
(b)

Figure 1.1

Figure 1.2 Human auditory pathways

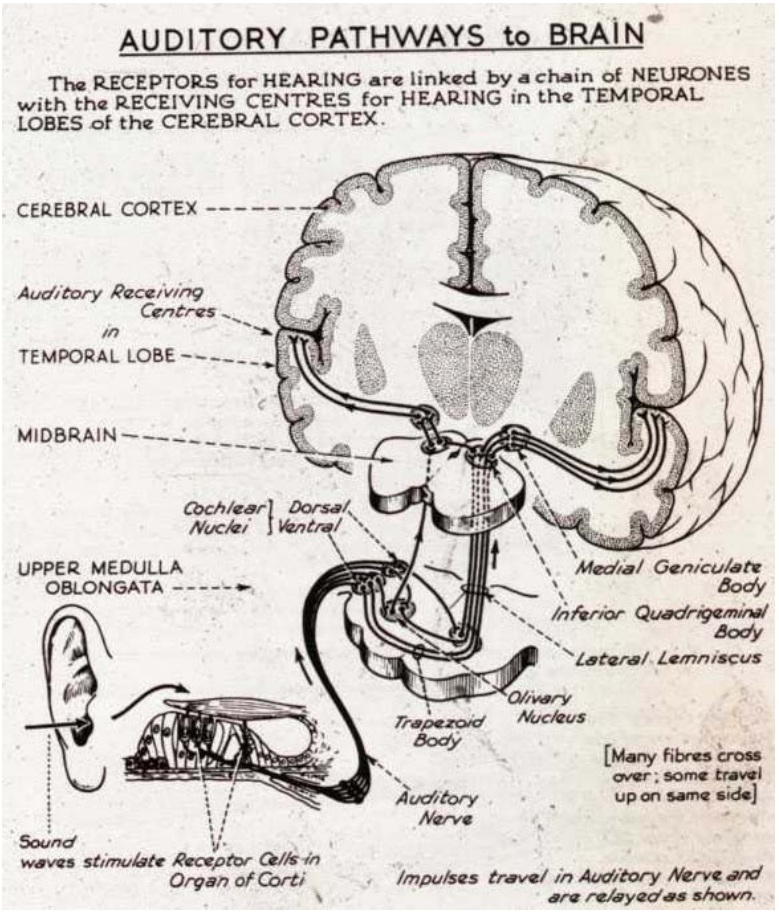

AUDITORY PATHWAYS to BRAIN
The RECEPTORS for HEARING are linked by a chain of NEURONES with the RECEIVING CENTRES for HEARING in the TEMPORAL LOBES of the CEREBRAL CORTEX.
CEREBRAL CORTEX
Auditory Receiving Centres in TEMPORAL LOBE
MIDBRAIN
Cochlear Nuclei
Dorsal
Ventral
UPPER MEDULLA OBLONGATA
Medial Geniculate Body
Inferior Quadrigeminal Body
Lateral Lemniscus
Olivary Nucleus
Trapezoid Body
[Many fibres cross over; some travel up on same side]
Auditory Nerve
Sound waves stimulate Receptor Cells in Organ of Corti
Impulses travel in Auditory Nerve and are relayed as shown.

Figure 1.2

Figure 2.1 Top-down magnetic field topography. Magnetic field topography of auditory evoked responses is taken from 30 representative MEG sensors: (A) the topography of standard stimuli evoked responses of young and old subjects; (B) the topography of target stimuli evoked responses of young and old subjects.

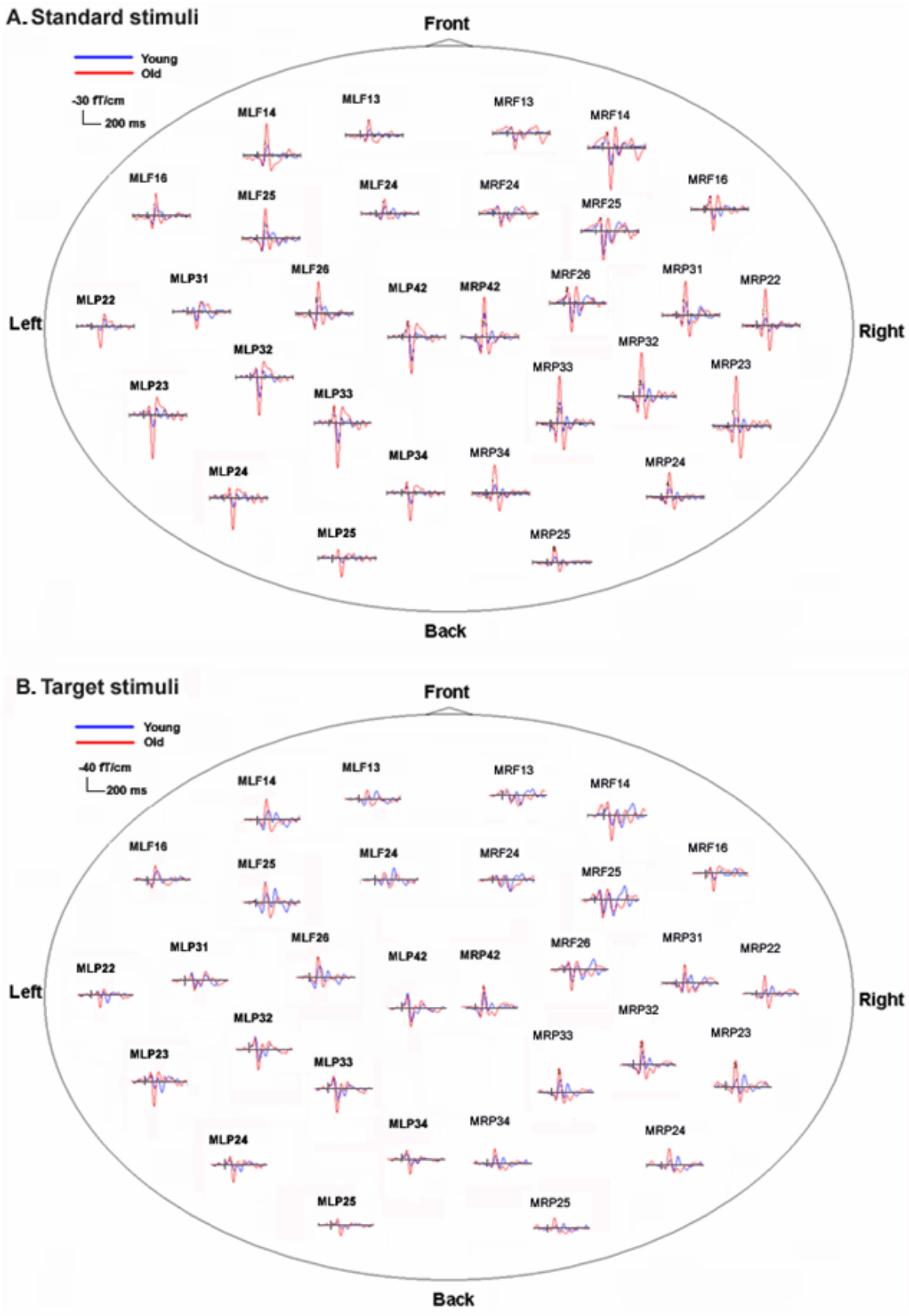
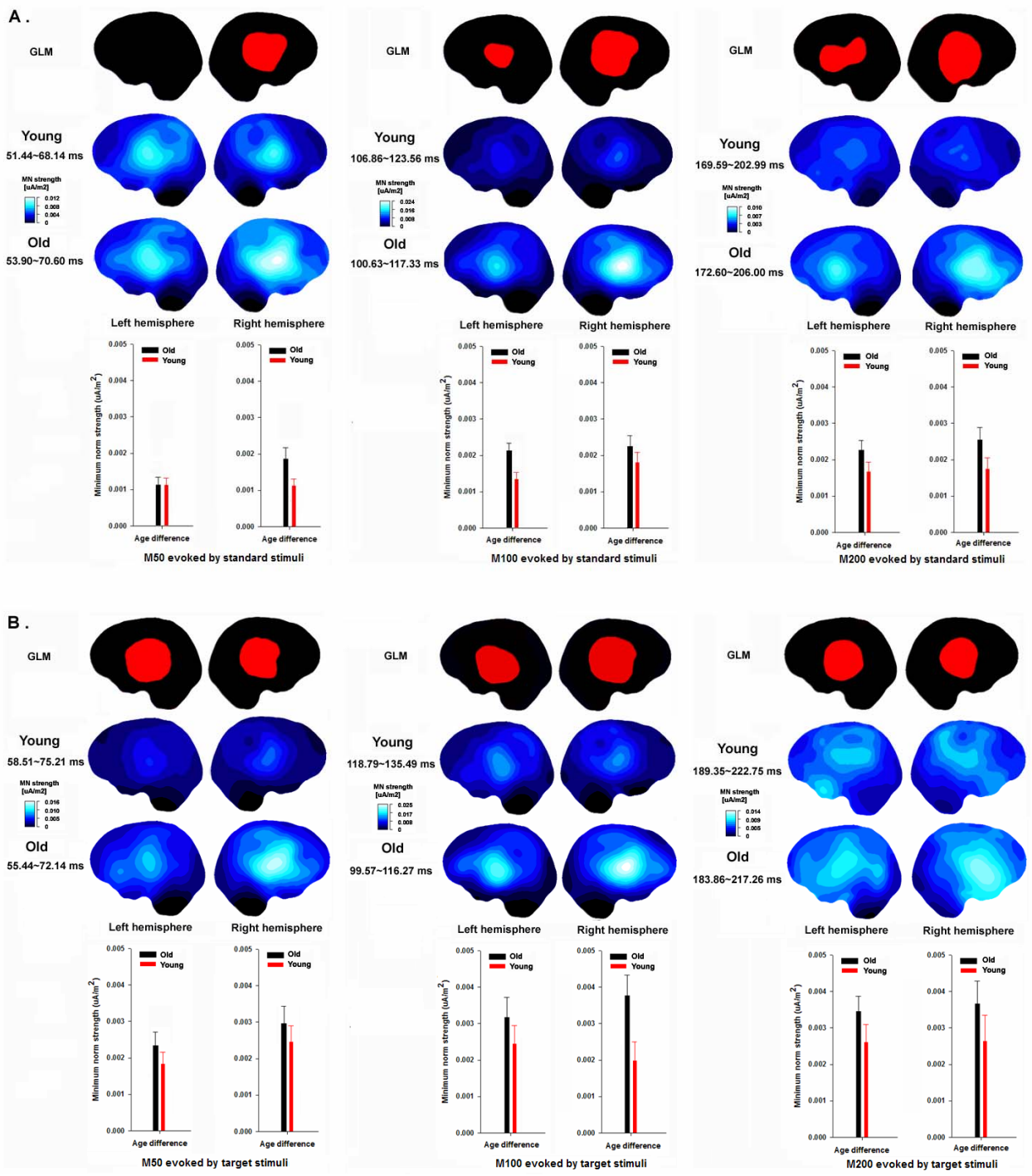

A. Standard stimuli
Front
Young
Old
-30 fT/cm
200 ms
MLF14
MLF13
MRF13
MRF14
MLF16
MLF25
MLF24
MRF24
MRF25
MRF16
MLP31
MLF26
MLP42
MRP42
MRF26
MRP31
MRP22
MLP22
Left
Right
MLP32
MRP32
MRP33
MRP23
MLP23
MLP33
MLP34
MRP34
MRP24
MLP24
MLP25
MRP25
Back
B. Target stimuli
Front
Young
Old
-40 fT/cm
200 ms
MLF14
MLF13
MRF13
MRF14
MLF16
MLF25
MLF24
MRF24
MRF25
MRF16
MLP31
MLF26
MLP42
MRP42
MRF26
MRP31
MRP22
MLP22
Left
Right
MLP32
MRP32
MRP33
MRP23
MLP23
MLP33
MLP34
MRP34
MRP24
MLP24
MLP25
MRP25
Back

Figure 2.1

Figure 3.1 Age associated differences on M50, M100 and M200. (A) Sources of auditory responses M50, M100 and M200 evoked by standard stimuli. The 1st row shows the cortical sources bearing significant age differences in strength; the 2nd and 3rd row show young and old subjects' L2 minimum norm results projected on MR structural images, respectively; the 4th row shows the mean source strength and standard errors of sources bearing significant age difference. (B) Sources of auditory responses M50, M100 and M200 evoked by target stimuli. The 1st row shows the cortical sources bearing age significant in strength; the 2nd row and 3rd show young and old subjects' L2 minimum norm results projected on MR structural images, respectively; the 4th row shows the mean and standard error of source strength from the sources bearing significant age difference.

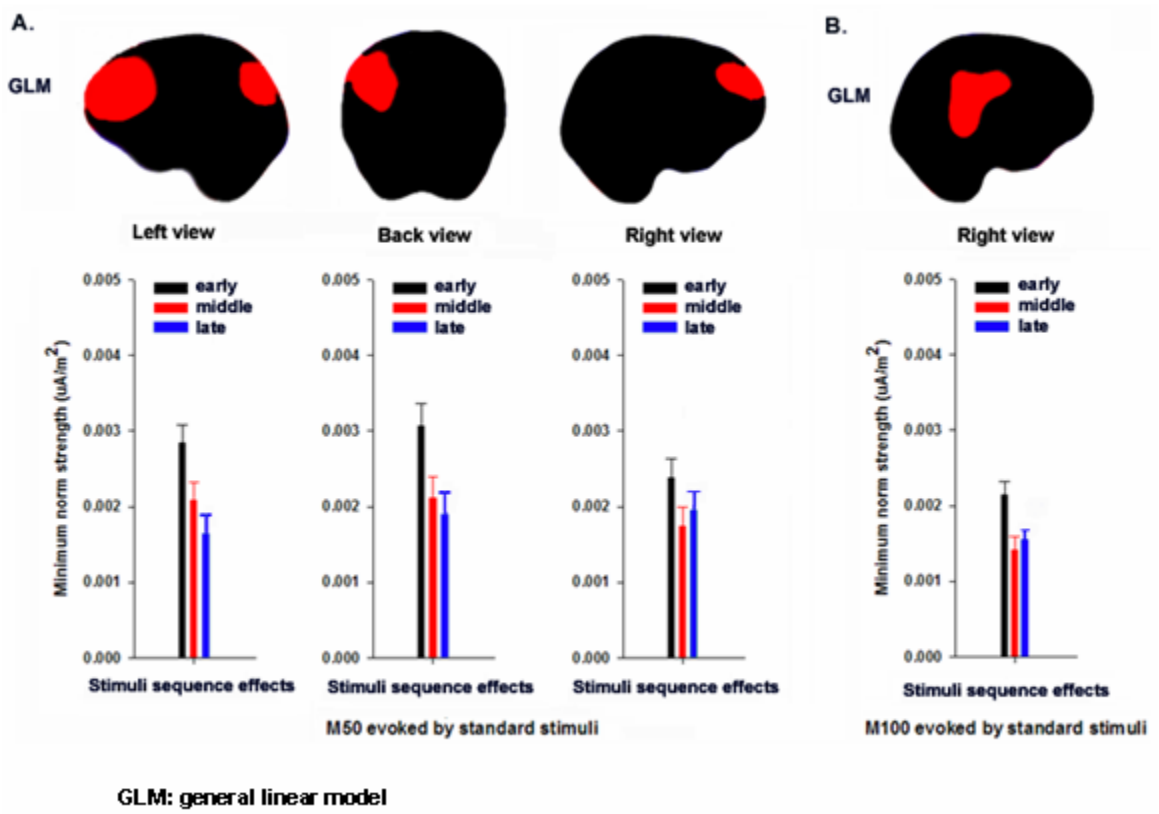


GLM: general linear model **Young: young subjects**

MN: minimum norm **Old: old subjects**

Figure 3.1

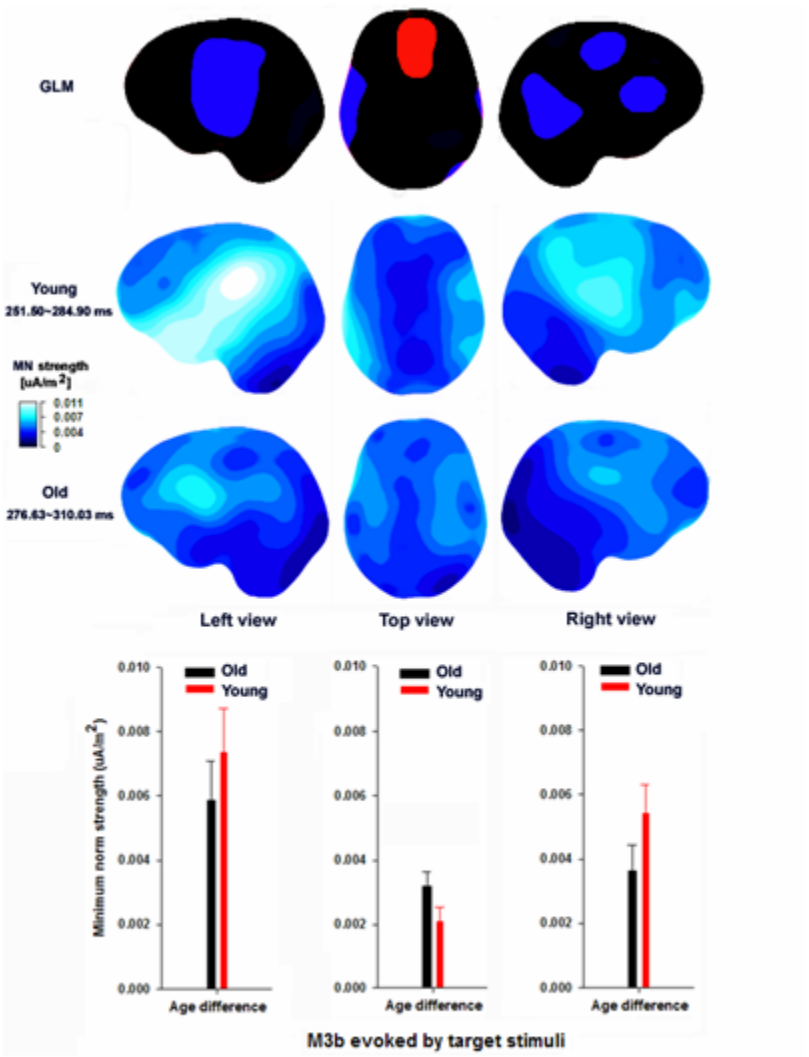
Figure 3.2 Stimuli rate effects on M50 and M100. (A) The 1st row shows the cortical sources bearing significant stimulus rate effects; the 2nd row shows the mean source strength and standard error of sources bearing significant stimulus rate effects.



GLM: general linear model

Figure 3.2

Figure 3.3 Age associated differences on M300. The 1st row shows the cortical sources bearing significant age difference in strength; the 2nd and 3rd row show young and old subjects' L2 minimum norm results projected on MR structural images, respectively; the 4th row shows the mean source strength and standard error of sources bearing significant age difference.



GLM: general linear model
MN: minimum norm
Young: young subjects
Old: old subjects

Figure 3.3