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Effects of aging on neuromagnetic mismatch responses to pitch changes

Chia-Hsiung Cheng[a,e,f,i], Sylvain Baillet[i], Fu-Jung Hsiao[a,h], Yung-Yang Lin[a,b,c,d,e,f,g,*]

[a] Institute of Brain Science, National Yang-Ming University, Taipei, Taiwan
[b] Department of Neurology, National Yang-Ming University, Taipei, Taiwan
[c] Institute of Physiology, National Yang-Ming University, Taipei, Taiwan
[d] Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan
[e] Laboratory of Neurophysiology, Taipei Veterans General Hospital, Taipei, Taiwan
[f] Integrated Brain Research Laboratory, Taipei Veterans General Hospital, Taipei, Taiwan
[g] Department of Neurology, Taipei Veterans General Hospital, Taipei, Taiwan
[h] Department of Education and Research, Taipei City Hospital, Taipei, Taiwan
[i] Dynamic Neuroimaging Laboratory, McConnell Brain Imaging Center, Montreal Neurological Institute, McGill University, Montreal, Canada

HIGHLIGHTS

- Effects of aging on MMNm were examined by MEG using distributed source modeling.
- A network of fronto-temporo-parietal regions underlying MMNm was identified.
- A widely distributed aging-related reduction of cortical responses to MMNm was found.
- These data suggest a decline in auditory sensory memory associated with aging.

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ABSTRACT

Although aging-related alterations in the auditory sensory memory and involuntary change discrimination have been widely studied, it remains controversial whether the mismatch negativity (MMN) or its magnetic counterpart (MMNm) is modulated by physiological aging. This study aimed to examine the effects of aging on mismatch activity to pitch deviants by using a whole-head magnetoencephalography (MEG) together with distributed source modeling analysis. The neuromagnetic responses to oddball paradigms consisting of standards (1000 Hz, $p = 0.85$) and deviants (1100 Hz, $p = 0.15$) were recorded in healthy young ($n = 20$) and aged ($n = 18$) male adults. We used minimum norm estimate of source reconstruction to characterize the spatiotemporal neural dynamics of MMNm responses. Distributed activations to MMNm were identified in the bilateral fronto-temporo-parietal areas. Compared to younger participants, the elderly exhibited a significant reduction of cortical activation in bilateral superior temporal guri, superior temporal sulci, inferior fontal gyri, orbitofrontal cortices and right inferior parietal lobules. In conclusion, our results suggest an aging-related decline in auditory sensory memory and automatic change detection as indexed by MMNm.

1. Introduction

During physiological aging, multiple cognitive aspects, including episodic memory, speed of information processing, visuospatial abilities and executive functions, tend to decline. These aging-related neuropsychological deficits have been related to both structural and functional alterations in the brain [22]. Most importantly, these changes also have detrimental influences on early-stage perceptual processing, e.g., sensory memory, which plays an essential role in the higher-order and subsequent cortical operations [4,30]. Given that physiological aging is associated with a risk of developing cognitive impairment, it is therefore crucial, clinically and scientifically, to obtain markers of aging-related changes in sensory memory.

Mismatch negativity (MMN) or its magnetic counterpart (MMNm) is a cerebral response to any discriminable change in repetitive auditory stimulation, and is generated in the absence of attention. It is a useful electrophysiological marker to evaluate the integrity of auditory sensory memory and automatic change detection [31,35,51]. Previous studies have shown significant changes in MMN or MMNm in various disease entities such as

* Corresponding author at: Department of Neurology, Taipei Veterans General Hospital (No. 201, Sec. 2, Shih-Pai Rd.), Taipei 112, Taiwan. Tel.: +886 2 28757398; fax: +886 2 28757579.
E-mail addresses: yylin@ym.edu.tw, g2000kev@gmail.com, yylin@vghtpe.gov.tw (Y.-Y. Lin).

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Alzheimer's disease [11], schizophrenia [26,47], dyslexia [43] and Parkinson's disease [34,44]. Moreover, several studies have tried to assess an alteration of MMN in physiological aging. However, it remains inconclusive whether the amplitude of MMN would be modulated by aging. Up to date, 16 event-related potential studies demonstrated a prominent MMN reduction in the elderly compared to the young group [1,2,6,7,12,13,17,23,24,27,29,30,38,41,42,50], whereas 12 studies reported on non-significant MMN attenuation in the elderly adult population [3,15,18–20,28,33,36,37,39,42,48]. To reconcile these findings, we capitalized on the excellent temporal resolution and reasonable spatial resolution of magnetoencephalography (MEG) to study the aging-related alterations of the spatiotemporal neural dynamics underlying MMNm.

2. Materials and methods

2.1. Subjects

Due to the possible effects of gender differences on the cerebral responses, 20 young male adults (20–34 years of age, mean 24.6) and 18 healthy elderly male adults (59–82 years of age, mean 68.8) participated in this study. Careful examination verified that every subject had normal hearing ability without history of neurological deficits. The older participants scored ≧27 on the Mini-Mental Status Exam. Written informed consent verified by the Institutional Review Board of Taipei Veterans General Hospital was obtained from all subjects.

2.2. Stimuli and magnetic recording procedures

Auditory stimuli were 350-ms sine-wave tones, binaurally delivered through plastic earphones. The absolute sound intensity was ~70–80 dB and ~75–85 dB in the young and elderly groups, respectively. The oddball block consisted of standard stimuli (1000 Hz, $p = 0.85$) and deviants stimuli (1100 Hz, $p = 0.15$) with a stimulus onset asynchrony of 1000 ms.

The magnetic responses were recorded with a 306-channel whole-head MEG instrument (Vectorview, Elekta-Neuromag, Helsinki, Finland) in a magnetically shielded room. The epoch duration was 900 ms, including a 100 ms prestimulus baseline. The online bandpass filter and sampling rate were set to [0.1, 130] Hz and 400 Hz, respectively. Electro-oculogram (EOG) electrodes were attached above the left orbit and below the right orbit, to monitor eye movements and blinks. Epochs contaminated by eye blinks (EOGs > 150 μV) were discarded. In each subject, at least 100 artifact-free deviants were collected for further analyses. All the participants were instructed to focus on watching a silent movie they had selected and to ignore the auditory stimuli.

2.3. Source estimation

The averaged data were off-line filtered with a bandpass of [1, 30] Hz [9,10]. The MMNm component in the event-related MEG average was determined by subtracting the responses to standards from those to deviants.

The modeling of the cortical spatiotemporal dynamics of MMNm was obtained with Brainstorm [46]. The segmentation of head tissues from individual T1-weighted Magnetic Resonance Imaging (MRI) volume data was obtained with BrainVisa (http://brainvisa.info/). The forward modeling of MEG measures was completed using an overlapping-sphere analytical model. For each participant, cortically constrained source imaging was performed using the depth-weighted minimum norm estimate (MNE) [5,21] model of Brainstorm, with default parameter settings, over a set of ~7500 elementary current dipoles distributed over the individual cortical envelope. The individual source maps were geometrically registered to the Montreal Neurological Institute brain template (Colin27) using Brainstorm's multilinear registration technique, with default parameters.

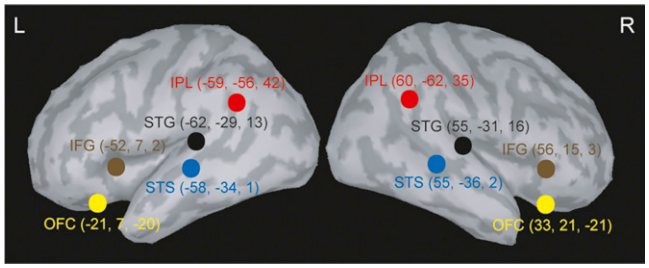

Fig. 1. Selection of region of interests (4–5 cm^2) on Montreal Neurological Institute Colin27 brain template. The numbers in the brackets show the MNI coordinates. STG, superior temporal gyrus; STS, superior temporal sulcus; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; OFC, orbitofrontal cortex.

The time-resolved magnitude of each elementary source was normalized to its fluctuations over baseline, yielding a set of *Z*-scored time series at each cortical location. The *Z* score values were rectified to detect absolute magnitude changes above baseline levels.

2.4. Selection of regions of interest

The MNE source maps were obtained for each participant and averaged onto the aligned cortical surface of the Colin27 brain template. Based on the grand-averaged waveform time series, a temporal window between 100 and 250 ms was selected in each region of interest (ROI) for further analysis. The definition of the anatomical ROIs was based on the prediction that MMNm generators would be located primarily in the temporal, frontal and parietal regions. A cluster of 30 cortical vertices corresponding to 4–5 cm^2, was manually selected to define each ROI (Fig. 1).

2.5. Statistical analysis

For a given ROI, between-group amplitude differences at each time point were compared using independent, two-tailed *t*-tests (Brainstorm). *p* values of < 0.05 were considered significant.

3. Results

3.1. Source distribution

Fig. 2 shows the grand-averaged MMNm waveforms recorded by the MEG sensor arrays and the corresponding spatiotemporal cortical source maps in young ($n = 20$) and elderly ($n = 18$) groups. In young adults, the superior temporal and frontal cortices were activated at ~100 ms and sustained throughout the whole epoch (100–250 ms). The activation of the right inferior parietal lobule emerged at 125 ms following temporal and frontal activity, and persisted for about 50 ms. The responses over the right hemisphere were larger than those over the left hemisphere. Neural activation in the elderly group demonstrated similar patterns, although with decreased activation strength compared to young participants. Also note that, in contrast to young participants, the left frontal regions were more activated than over the right frontal cortex in the elderly group.

3.2. ROI-based analysis

We identified five ROIs in each hemisphere from the grand-averaged source maps in the 100–250 ms time range: the superior temporal gyrus (STG), superior temporal sulcus (STS), inferior