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# Region-specific reduction of auditory sensory gating in older adults

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ABSTRACT

Aging has been associated with declines in sensory–perceptual processes. Sensory gating (SG), or repetition suppression, refers to the attenuation of neural activity in response to a second stimulus and is considered to be an automatic process to inhibit redundant sensory inputs. It is controversial whether SG deficits, as tested with an auditory paired-stimulus protocol, accompany normal aging in humans. To reconcile the debates arising from event-related potential studies, we recorded auditory neuromagnetic reactivity in 20 young and 19 elderly adult men and determined the neural activation by using minimum-norm estimate (MNE) source modeling. SG of M100 was calculated by the ratio of the response to the second stimulus over that to the first stimulus. MNE results revealed that fronto-temporo-parietal networks were implicated in the M100 SG. Compared to the younger participants, the elderly showed selectively increased SG ratios in the anterior superior temporal gyrus, anterior middle temporal gyrus, temporal pole and orbitofrontal cortex, suggesting an insufficient age-related gating to repetitive auditory stimulation. These findings also highlight the loss of frontal inhibition of the auditory cortex in normal aging.



## 1. Introduction

Physiological aging is associated with functional decline in various cognitive aspects, including sensory memory, processing speed, attention and executive function (Cheng, Baillet, Hsiao, & Lin, 2015; Cheng, Hsu, & Lin, 2013; Cheng & Lin, 2012; Hedden & Gabrieli, 2004). The inhibition modulation of cortical and subcortical neurons, which is affected by aging, plays an important role in the higher-hierarchical cerebral operations (Gazzaley, Cooney, Rissman, & D'Esposito, 2005). In addition, inhibition circuits have been reported to be involved in the regulation of sensory processing and neural oscillations (Alitto & Dan, 2010; Wehr & Zador, 2005). In the human auditory system, electrophysiological research has revealed a relationship between early-stage cortical inhibition to redundant sensory inputs and later-stage salience detection (Cheng, Wang, Hsu, & Lin, 2012; Kisley, Davalos, Engleman, Guinther, & Davis, 2005; Kisley, Noecker, & Guinther, 2004).

Auditory sensory gating (SG) or repetition suppression, referring to the brain's ability to pre-attentively suppress irrelevant sensory inputs, is considered as a protective mechanism against flooding of the higher cortical centers with unnecessary information (Boutros & Belger, 1999; Cheng & Lin, 2013; Todorovic, van Ede, Maris, & de Lange, 2011). Technically, SG is measured as the amplitude ratio of Stimulus 2-evoked responses (R2) over Stimulus 1-evoked responses (R1). A larger ratio indicates a less suppression in the cortex. SG of P50 and/or N100 has received considerable interest because of its potential application in clinical research, such as schizophrenia (Brenner et al., 2009; Clementz, Geyer, & Braff, 1998; Light, Geyer, Clementz, Cadenhead, & Braff, 2000; Patterson et al., 2008; Smith et al., 2010), traumatic brain injury (Arciniegas et al., 2000), migraine (Ambrosini, De Pasqua, Afra, Sandor, & Schoenen, 2001; Siniatchkin, Kropp, & Gerber, 2003) and Alzheimer's disease (Cancelli et al., 2006; Jessen et al., 2001;

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Thomas et al., 2010). However, the evidence regarding the effects of aging on auditory SG remains extremely limited and controversial. Kisley and colleagues found a significant age-related decline of auditory N100 SG (Kisley et al., 2005). Another report also showed that the elderly tended to have a greater difficulty in inhibiting redundant sensory inputs, as indexed by the N100/P200 complex (Boutros et al., 2000). In contrast, two other studies revealed the similar SG ratios between younger and older groups in terms of P50 and N100 components (Gmehlin, Kreisel, Bachmann, Weisbrod, & Thomas, 2011; Thomas et al., 2010).

Compared to the P50, examining SG of N100 (or its magnetic counterpart, M100) is growing promising in neuropsychiatric and neurological disorders due to several reasons. First, N100/M100 is the dominant component of auditory evoked responses and could be reliably detected in every individual in terms of source estimation (Godey, Schwartz, de Graaf, Chauvel, & Liegeois-Chauvel, 2001). Secondly, compared to P50, previous studies have demonstrated a better test–retest reliability in N100 (Fuerst, Gallinat, & Boutros, 2007; Rentzsch, Jockers-Scherubl, Boutros, & Gallinat, 2008). Thirdly, although neural correlates of P50 SG have been largely explored (Boutros, Gjini, Eickhoff, Urbach, & Pflieger, 2013; Grunwald et al., 2003; Korzyukov et al., 2007), knowledge about the circuitry of N100 SG remains poorly understood.

While bilateral temporal regions have been considered as main neural generators of auditory P50/N100 SG, recent functional magnetic resonance imaging and event-related potential (ERP) studies disclosed the frontal/prefrontal contribution in paired-stimulus or short-term habituation paradigms (Grau, Fuentemilla, & Marco-Pallares, 2007; Grunwald et al., 2003; Korzyukov et al., 2007; Mayer et al., 2009; Oranje, Aggernaes, Rasmussen, Ebdrup, & Glenthoj, 2013; Weiland, Boutros, Moran, Tepley, & Bowyer, 2008; Weisser et al., 2001). In addition, there is ample behavioral and neuroimaging evidence supporting the hypothesis of frontal aging, which postulates frontal/prefrontal cortex is particularly vulnerable to physiological aging (Tisserand & Jolles, 2003; West, 1996). However, up to the present, the frontal role of age-related auditory SG has not been well studied. Since aging *per se* is one of key factors leading to mild cognitive impairments, it merits a clearer understanding of functional reorganization and physiological state during late life, particularly in the pre-attentive condition.

To reconcile the previous ambiguous ERP results, we capitalized on the excellent temporal resolution and reasonable spatial resolution of magnetoencephalography (MEG) to assess whether auditory SG is modulated by physiological aging. Specifically, this study aimed (1) to determine the spatiotemporal dynamics of auditory responses to paired-stimulus paradigms by using distributed minimum norm estimate (MNE) source modeling, and (2) to examine whether auditory M100 SG is modulated by physiological aging.

## 2. Materials and methods

### 2.1. Participants

Due to the potential impacts of gender differences on the auditory SG (Hetrick et al., 1996), 20 young (20–30 years old, mean age 24.0) and 19 elderly (60–82 years old, mean age 69.5) male adults participated in this study and were paid for their time. Young adults were recruited from National Yang-Ming University. Old adults were recruited through advertisements posted at senior citizen centers, bulletin board system on Taipei Veterans General Hospital and National Yang-Ming University. The older participants scored high on the Cognitive Abilities Screening Instrument (CASI; mean 92.3, standard error of the mean [SEM] 0.90) (Lin et al., 2002). All subjects were right-handed. None of them had hearing problems, and none had neurological or psychiatric disorders, as determined by a careful examination. They also refrained from smoking for at least 12 h prior to MEG recordings. The Institutional Review Board of the Taipei Veterans General Hospital approved the protocol, and informed consent was obtained from all subjects.

### 2.2. Auditory stimulation and MEG recordings

Auditory stimuli were 800 Hz click-like tones (duration = 20 ms, including 5 ms rise and fall times), binaurally delivered through plastic earphones at the intensity of 60–70 dB above the subjects' hearing threshold. The paired-stimulus paradigm was presented with inter-stimulus intervals (ISIs) of 500 ms and inter-pair intervals of 8 s. During the experiment, subjects were asked to concentrate on watching a silent movie and ignore the auditory stimuli.

Auditory evoked fields (AEFs) were recorded by means of a whole-head 306-channel MEG (Vectorview™, Elekta Neuromag, Helsinki, Finland). The data from planar gradiometers of this device, which detect the largest signal directly above the activated cerebral areas (Hamalainen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993; Hari, Levanen, & Raij, 2000; Lin et al., 2007), were analyzed. Four head indicator coils were attached to the scalp, and their locations were detected by measuring the magnetic fields produced by the currents fed into them. The coil locations in relation to the anatomical landmarks (left pre-auricular point, right pre-auricular point, and nasion) were determined with a 3D digitizer.

For AEF recordings, the on-line bandpass and digitization rate were [0.1,200] Hz and 500 Hz, respectively. The analysis period was 500 ms, including a 100-ms pre-stimulus baseline. Epochs contaminated by prominent electro-oculograms (EOGs, >150 μV) and MEG artifacts (>3000 fT/cm) were automatically rejected from averaging. A total of at least 100 artifact-free responses to each stimulus type were averaged on-line.

### 2.3. Magnetic source imaging

The AEFs were digitally filtered with a bandpass [1,30] Hz offline (Cheng et al., 2010), with a 100-ms baseline correction. The time interval of M100 component was determined based on the grand-averaged waveforms.

The spatiotemporal dynamics of cortical sources were performed by using depth-weighted MNE (Baillet, Mosher, & Leahy, 2001; Hamalainen & Ilmoniemi, 1994) implemented in the Brainstorm software (Baillet, Friston, & Oostenveld, 2011; Tadel, Baillet, Mosher, Pantazis, & Leahy, 2011). The segmentation of head tissues from individual T1-weighted Magnetic Resonance Imaging (MRI, GE Discovery MR 750 3T with TR 9.4 ms, TE 4 ms, recording matrix 256_256 pixels, field of view 256 mm, slice thickness 1 mm) volume data was obtained with BrainVisa (http://brainvisa.info/). The representation of folded cortical surface was used to resolve the forward problem by applying an overlapping-sphere model, which derives the strength of a set of electric dipoles located at the cortical surface (Huang, Mosher, & Leahy, 1999). Cortically constrained MNE was computed for each participant with a source space consisting of ~15,000 elementary current dipoles over the cortex. Individual source map was then geometrically registered to the Montreal Neurological Institute (MNI) Colin27 brain template using Brainstorm's multilinear registration technique, with default parameters.

The time series of each dipole was normalized to the baseline noise, yielding a *Z*-score map (Cheng, Baillet, Hsiao, & Lin, 2013; Cheng, Chan, Baillet, & Lin, 2015; Gross et al., 2013). Absolute *Z*