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Lack of correlation between phonetic magnetic mismatch field and plasma D-serine levels in humans

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HIGHLIGHTS

- First study to examine a correlation between phonetic magnetic mismatch field (MMF) and plasma D-serine (an intrinsic co-agonist of glycine binding sites on NMDA receptors) in humans.
- We did not observe a significant correlation between MMF power/latency and plasma serine levels.
- Our study did not indicate that the presented level of D-serine could influence MMF in humans.

ABSTRACT

Objective: Uncovering molecular bases for auditory language processing in the human brain is a fundamental scientific challenge. The power and latency of the magnetic mismatch field (MMF) elicited by phoneme change, which are magnetoencephalographic indices of language function in its early stage of information processing, are theoretically thought to be modulated by *N*-methyl-D-aspartate-type glutamate receptor (NMDAR) function, but no study has yet assessed this possibility. We have thus sought to demonstrate an association between phonetic MMF power/latency and levels of plasma D-serine, an intrinsic co-agonist of glycine binding sites on NMDAR, in adults.
Methods: The MMF response to phoneme changes was recorded using 204-channel magnetoencephalography in 61 healthy, right-handed, Japanese adults. Plasma levels of D- and L-serine were measured for each participant.
Results: We did not find a significant correlation between MMF power/latency and plasma serine levels.
Conclusions: Despite a sufficient sample size, we failed to find an association between the physiological markers of the early stage of information processing of language in the auditory cortex and biomarkers indexing glutamatergic function.
Significance: Our study did not indicate that a molecular index of glutamatergic function could be a surrogate marker for the early stage of information processing of language in humans.

1. Introduction

Language processing is crucial for human social life. However, the molecular basis of physiological responses of language processing has remained an essential challenge in the neurobiology of language, because language processing cannot be investigated by animal studies, and invasive human studies are limited by ethical considerations. Language processing ability, in its early stage of

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information processing, can be neurophysiologically indexed by event-related potentials (ERPs) elicited by change detection of speech sounds, called mismatch negativity (MMN). In response to a tonal change, MMN (Näätänen et al., 1978) is elicited by subtracting ERPs in response to auditory stimuli (which are rare in probability and deviant in duration, frequency, or intensity) from ERPs in response to frequent, standard stimuli. MMN is maximal approximately 150–200 ms following stimulus onset, and is thought to index preattentive change detection process (Alho, 1995; Näätänen, 1995). MMN can be measured not only by electroencephalography (EEG), but also by magnetoencephalography (MEG), which is also referred to as the magnetic mismatch field (MMF). An MMN or MMF was also found to be elicited by changes in speech sounds and has been considered to be a sensitive marker of language-specific auditory processing (Näätänen et al., 1997). Moreover, MMN can index learning-induced neural plasticity, because language and speech training improve the reduced MMN observed in developmental disorders (Näätänen et al., 2012).

When assessing language-related speech-sound processing, the MMF has an advantage over the EEG recording of MMN. The MEG can more sensitively detect electric signals tangential but not radial to the scalp, which leads to an advantage in selectively identifying mismatch activity arising from the superior temporal gyrus (STG; Alho, 1995; Rosburg et al., 2005). Moreover, signals from the MEG are not influenced by volume conductance of the scalp, skull, intracranial structures, or cerebrospinal fluid. This characteristic enables the detection of signals from left and right auditory cortices independently, which may be crucial for assessing language-related activity in the temporal lobe.

MMN is influenced by the *N*-methyl-d-aspartate type glutamate receptor (NMDAR) in primates (Javitt et al., 1996; Gil-da-Costa et al., 2013) and in humans (Rosburg and Kreitschmann-Andermahr, 2016). In human subjects, meta-analysis has indicated that ketamine, an NMDAR antagonist, attenuates the amplitude of MMN and increases latency of MMN during both duration- and frequency-change sequences (Rosburg and Kreitschmann-Andermahr, 2016). Although not directly assessing NMDAR function by pharmacological challenge, supporting results have been reported in recent studies showing that phonetic MMF power was influenced by variations in the metabotropic glutamate receptor 3 (*GRM3*) gene in healthy adults (Kawakubo et al., 2011). Higher glutamate concentration levels as measured by 1H-magnetic resonance spectroscopy (MRS) were associated with shorter latency of MMN (Kompus et al., 2015). These findings, together with robustly replicated findings of reduced MMN/MMF amplitude/power in response to tonal (Umbricht and Krljes, 2005; Erickson et al., 2016) and phonetic (Kasai et al., 2002, 2003) changes in patients with schizophrenia, are compatible with the glutamatergic neurotransmission hypothesis of schizophrenia. Furthermore, previous investigations indicated that d-serine, which is an intrinsic co-agonist of NMDAR, showed a reduction in blood and cerebrospinal fluid in schizophrenia (Hashimoto et al., 2003, 2005). However, no study has explored the correlation between MMN/MMF in response to phonetic change and body fluid levels of d-serine in adults.

The response of an MMN or MMF to phonetic change has been also applied to autism spectrum disorders (ASD), since a core feature of this developmental disorder lies in communication deficits. Children with ASD showed a delayed latency of MMF to speech sounds in the right STG (Jansson-Verkasalo et al., 2003), and adults with ASD showed similar findings in the left STG (Kasai et al., 2005). Roberts et al. (2011) demonstrated that the prolonged peak latency of MMF to phoneme change observed in ASD children was most evident in those who had a comorbid language impairment, a finding which validates the usefulness of the peak latency of phonetic MMF as a biomarker for language processing ability (Näätänen and Kujala, 2011). A recent review (Zheng et al., 2017) showed that only one study that has investigated body fluid level of d-serine in ASD did not find an abnormality.

Accordingly, we explored an association between power/latency of phonetic MMF, an index of early-stage language processing, and blood d-serine concentration in healthy adults. We predicted that individual variation in NMDAR function would be correlated with the early-stage neural representation of speech sound processing, as indexed by MMF. If we are able to support the prediction, it may provide a clue to further clinical research regarding therapeutic intervention, including amelioration of language processing dysfunction by d-serine in neuropsychiatric disorders such as schizophrenia and ASD.

2. Methods

2.1. Participants

61 healthy Japanese adults (31 men, 30 women; average age: 29.7 [SD = 7.7] years [range: 21–55]) participated in the study. Mean years of education were 17.1 [Standard deviation = 1.7], and mean IQ was 111.7 [S.D. = 7.5]. Exclusion criteria were described in detail in a previous study (Kawakubo et al., 2011). The ethics committee, Faculty of Medicine, The University of Tokyo (MEG experiment, No. 784-2; plasma serine measurement, No. 2094-5) approved the study. Written informed consent was obtained for all participants.

2.2. MMF power/latency and plasma serine measurements

MEG measurement procedure was described in detail in our previous paper (Suga et al., 2016). The stimulus sequence consisted of standard (probability, 90%; Japanese vowel /a/ [80 dB SPL]; duration, 250 ms; rise/fall time, 10 ms) and deviant (p, 10%; Japanese vowel /o/ [duration, 250 ms]) stimuli. The stimulus onset asynchrony (SOA) was 445 ± 15 ms. We conducted the experiments in the afternoon (from 2 to 3p.m.) for all participants. MEG measurements were conducted in a magnetically shielded room using VectorView (Elekta Neuromag Oy, Helsinki, Finland). The sensors (306 in total) were arranged in triplets of two planar gradiometers (204 sensors) and a magnetometer at 102 locations. The authors did not use signals from the magnetometer.

As previously described (Suga et al., 2016), the recorded data were filtered online with a band-pass filter of 0.03–100 Hz, digitized at a sampling rate of 512 Hz, and averaged online separately for standard and deviant stimuli. The duration of the averaging period was 400 ms, including an 80-ms prestimulus baseline. Trials with EOG movement exceeding 150 μV or MEG values exceeding 3000 fT/cm were excluded from the analysis. The number of accepted responses for deviant stimuli was above 100 for all subjects. The averaged data were further filtered offline with a band-pass filter of 1–20 Hz.

The MMF was identified by subtraction of the evoked MEG of the standard stimuli from those of the deviant stimuli. The MMF strength was indexed by the magnetic global field power (mGFP), calculated separately for each hemisphere. mGFP was calculated separately for each hemisphere and defined as the root mean square (RMS) of the differences over 54 sensors (27 locations) on the temporal region (Kasai et al., 2003; Takei et al., 2009). The peak latency of the MMF was identified by the curve of mGFP for each hemisphere. The mGFP at peak latency was the index of MMF power for each participant.

Blood samples were drawn from each participant just before the MEG session (2 p.m.). Plasma absolute levels of d- and l-serine, and relative d-serine level [100 × (d-serine)/(d-serine + l-serine)] (%),