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# Longitudinal changes in the mismatch field evoked by an empathic voice reflect changes in the empathy quotient in autism spectrum disorder☆

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ABSTRACT

Autism spectrum disorders (ASDs) are neurodevelopmental conditions with impairments in social communication and interaction. Empathy is the ability to understand and share another person's inner life, and it is an essential process in social cognition, which is deficient in ASD. The mismatch field (MMF) has been used as a neurophysiological marker for the automatic detection of changes in auditory stimuli. In the present study, we focused on long-term changes in MMF evoked by an empathic voice and changes in the empathy quotient (EQ) in ASD during an 8-week clinical trial using oxytocin (OT). Ten males with ASD without intellectual disability participated in this pilot study. The results demonstrated a significant positive correlation between the change in the MMF amplitude in the auditory cortex (i.e., right banks of the superior sulcus) and the change in the EQ score during the 8-week clinical trial, whereas no significant change was observed in the MMF amplitude or EQ score after the administration period of OT. Although we cannot conclude that the observed relationships were caused by OT's effect or by natural changes, our results suggest that MMF evoked by social voice can be a state-dependent marker of empathic abilities in male adults with ASD.

## 1. Introduction

Empathy is the ability to understand and share another person's inner life, and it is an essential process in social cognition. Recent studies have focused on the difficulty of cognitive empathy (Baron-Cohen and Wheelwright, 2004; Mazza et al., 2014) and emotional empathy (Fridenson-Hayo et al., 2016; Trimmer et al., 2017) in individuals with ASD. It has been proposed that social interactive and communicative problems can be attributed to impairments in empathy (Baron-Cohen, 2002). Auditory mismatch negativity (MMN) or its magnetic mismatch field (MMF) (Sams, 1991) has been used as a neurophysiological marker for the integrity of auditory sensory memory and automatic change detection (Kujala et al., 2007). The sources of MMN have been identified as the bilateral temporal regions in the primary and secondary auditory cortices, with contributions from the frontal regions (Alho, 1995; Doring et al., 2016; Naatanen et al., 2007; Rinne et al., 2000). In healthy populations, the MMN/MMF is considered an indicator of change detection and has been used to probe speech discrimination (Eulitz and Lahiri, 2004; Mathiak et al., 2000; Naatanen et al., 1997; Tavabi et al., 2009). Based on the use of source-localizing methods, MMN/MMF has been reported to be generated by temporal and frontal lobe sources, with the former being associated with change detection and the latter with involuntary switching of attention to sound changes (Rinne et al., 2000). Intriguingly, in a recent EEG study, Hoyniak et al. (2017) reported that children ages 2–5 years with callous-uncaring traits showed reduced neural responses (i.e., MMN) to vocal fear (Hoyniak et al., 2017). Callous-unemotional traits are characterized by a lack of guilt and empathy, as well as low responsiveness to distress and fear in others. Korpilahti et al. (2007) also reported that latencies of MMN associated with affective speech

*Abbreviations:* ASD, autism spectrum disorder; OT, oxytocin; MMF, magnetic mismatch field; MEG, magnetoencephalography

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prosody were longer in individuals with Asperger syndrome than in the controls (Korpilahti et al., 2007). Thus, the auditory response (i.e., MMN/MMF) evoked by the human intentional voice must be related to the impairment of empathy in individuals with ASD. However, the relationship between longitudinal changes in brain auditory responses (i.e., MMF) evoked by voice with social intonation and changes in clinical symptoms of empathy in individuals with ASD is still unknown.

In this study, we hypothesized that longitudinal changes in brain auditory responses (i.e., MMF) which reflect the sensitivity to voice with social intonation is associated with the changes in clinical symptoms of empathy in individuals with ASD. We tested this hypothesis in our previous clinical trial (umin.ac.jp/ctr Identifier: UMIN000011077) using oxytocin (OT), which modulates complex social behaviours (De Dreu and Kret, 2016), such as empathy (Shamay-Tsoory et al., 2013). To verify this hypothesis in the present study, we used a magnetoencephalography (MEG) device. MEG allows an accurate, non-invasive identification of most auditory evoked response generators for the right and left hemispheres simultaneously due to spatially separated magnetic fields. Therefore, the MEG is the optimal device for investigating auditory evoked responses.

## 2. Methods

### 2.1. Participants

Ten males with ASD aged 23–41 years (mean [SD], 30.3 [5.8] years) participated in the experiment (Table 1). All participants were right-handed and native Japanese and had an IQ of greater than 70 (mean [SD] IQ, 102.2 [13.0]; IQ range 85–130), which was measured using the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 2008). An ASD diagnosis was based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (American Psychiatric Association, 2000) and the Autism Diagnostic Observation Schedule–Generic (ADOS) (Lord et al., 1989). Seven of these men were naïve to medical treatment for at least 6 months before the experiment. In three subjects, medication including a selective serotonin reuptake inhibitor (1 subject) and benzodiazepine (3 subjects) was suspended at least four weeks before MEG measurements. During this experimental period, none of the participants changed their treatment. Written informed consent was obtained prior to enrolment. The Ethics Committee of Kanazawa University Hospital and Hamamatsu University School of Medicine approved the methods and procedures used in this study, which was performed in accordance with the Declaration of Helsinki. The study was registered with the University Hospital Medical Information Network Clinical Trials Registry (number UMIN000011077). The participants were the same as those of a previously reported study (Hirosawa et al., 2017).

**Table 1**
Clinical variables for the pre-OT administration in participants.

| Number of participants | 10 |
|---|---|
| ADOS total score (range) | 13.3 (9–18) |
| AQ score (range) | 33.3 (14–48) |
| EQ score (range) | 19.6 (5–36) |
| RBS-R score (range) | 19.4 (1–47) |
| SDS score (range) | 49.5 (34–61) |
| STAI score (range) | 111.7 (75–137) |
| WHOQoL score (range) | 2.68 (1.5–3.7) |

Abbreviations: AQ, Autism-Spectrum Quotient; EQ, Empathy Quotient; RBSR, Repetitive Behavior Scale-Revised; SDS, Zung Self-Rating Depression Scale; SQ, Systemizing Quotient; STAI, State-Trait Anxiety Inventory; WAIS-R, Wechsler Adult Intelligence Scale; WHOQoL, World Health Organization Quality of Life.

### 2.2. Experimental design

The experiments were performed according to an open-label, single-arm, non-randomized, uncontrolled study. Following the first clinical assessments and image acquisition, the participants received 24 IU of intranasal OT (Syntocinon; Novartis, Basel, Switzerland) per day for 8 weeks.

### 2.3. Clinical assessment of empathy

To measure the participants' strength of interest regarding empathy, we used the empathy quotient (EQ) (Baron-Cohen and Wheelwright, 2004) before and after OT administration. This self-report questionnaire contains 40 empathy items and 20 filler/control items. On each empathy item, a person can score 2, 1, or 0; therefore, the EQ has a maximum score of 80 and a minimum of 0. A person who scores highly on this test would be considered a good empathizer: easily able to detect and be appropriately affected by other people's feelings. Since EQ was reported to be a reliable and valid way of measuring empathy via self-report in both healthy individuals and clinical populations (Lawrence et al., 2004), we employed this psychological measurement.

### 2.4. Auditory-evoked field stimuli and procedures

We used typical oddball sequences consisting of standard stimuli (230 times, 83%) and deviant stimuli (45 times, 17%) (Fig. 1). We used the Japanese syllable "ne" because this syllable is a sentence-ending particle in Japanese and conveys prosodic information (Anderson et al., 2007). The syllable "ne" expresses a speaker's request for acknowledgement or empathy from the listener (Kajikawa et al., 2004). This syllable can be pronounced in two different ways. A repetitive series of utterances of "ne" pronounced with a flat tone (/ne/) was used as the standard. This stimulus carries no intonational information. As a deviant stimulus, we used "ne" pronounced with a high falling tone (/Ne/), which carries intonational information that gives the listener a feeling of 'being spoken to' (Ueno et al., 2012; Yoshimura et al., 2013).

### 2.5. Magnetoencephalography recordings

Magnetic fields were measured using a whole-head MEG system for adults in a magnetically shielded room (Daido Steel, Nagoya, Japan) in the MEG Center of Ricoh Company, Ltd. in Japan. This system (MEG vision PQA160C; Yokogawa Electric Corporation, Kanazawa, Japan) employs 160 channels of axial gradiometers, where the coil diameter of the sensors is 15.5 mm and the baseline is 50.0 mm. Band-pass-filtered

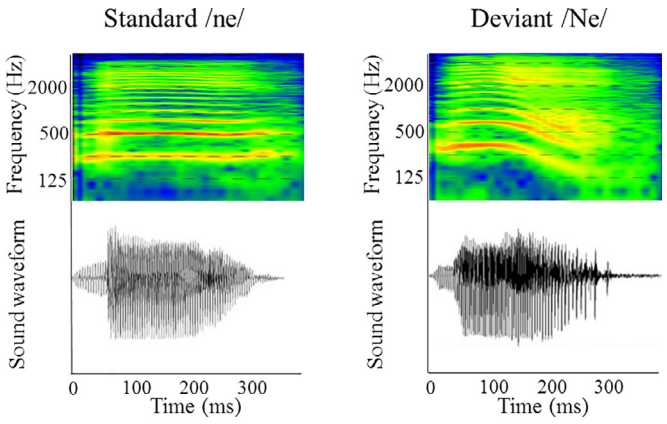


**Fig. 1.** Spectral and temporal characteristics of the stimulus items *standard /ne/* and *deviant /Ne/* are shown. Formants are indicated with red lines. Please note the near-flat contour for the *standard /ne/* (left) and the high falling contour for the *deviant /Ne/* (right).