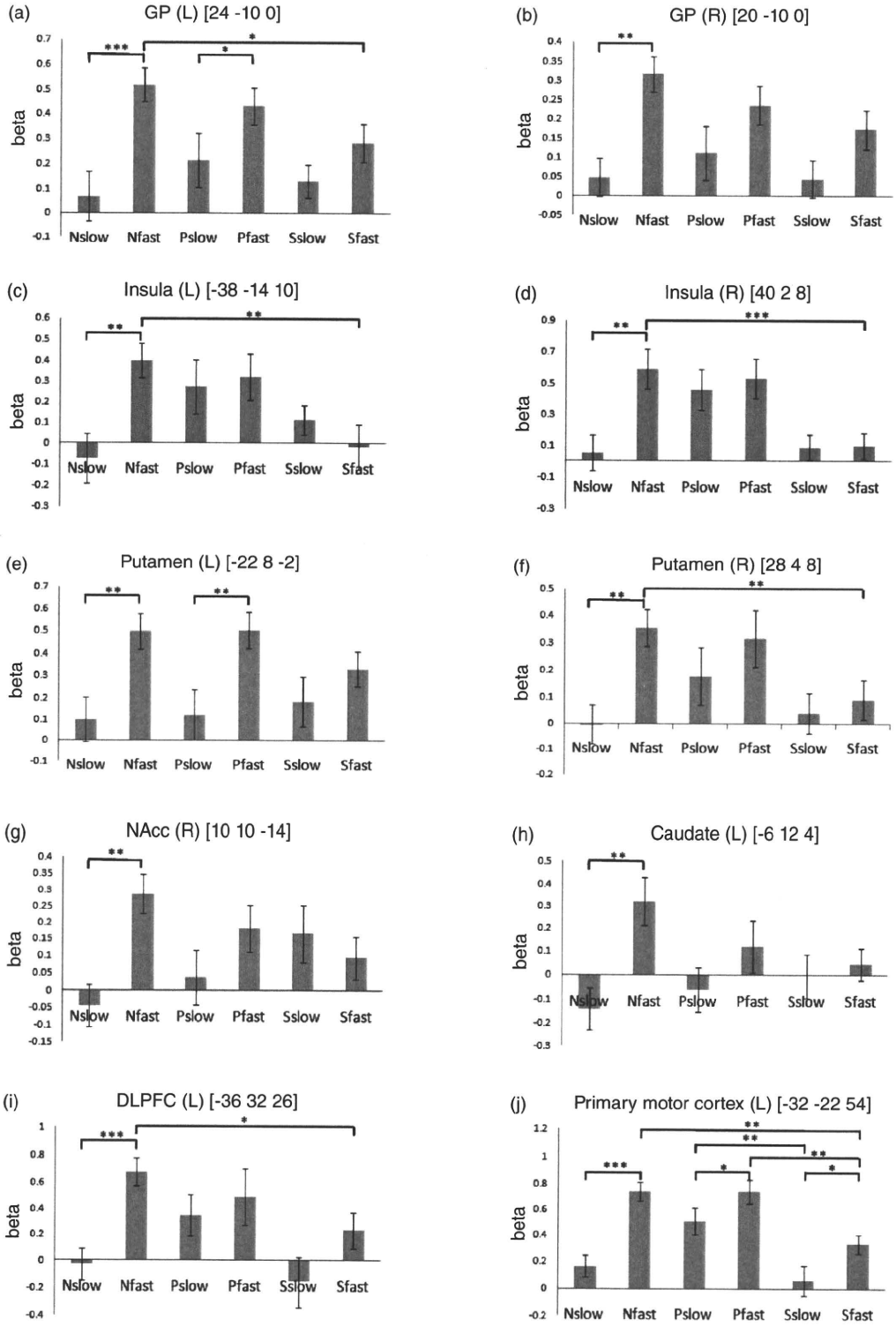

Figure 1. The mean beta values for the peak activation categorized by drug and reaction time type for the defined regions-of-interest. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$. Error bars show SEM. DLPFC, dorsolateral prefrontal cortex; GP, globus pallidus; L, left; NAcc, nucleus accumbens; R, right.

These results might partly come from the duration of drug administration because sufficient antidepressive effects of SSRI are not apparent normally until after 3–6 weeks of treatment. The increase in 5-HT produced by a single administration of SSRI not only stimulates the postsynaptic 5-HT receptors but also stimulates the somatodendritic inhibitory 5-HT_{1A} autoreceptors and presynaptic 5-HT_{1B} and 5-HT_{1D} autoreceptors. This varied activity could produce a net reduction in the activity of the 5-HT system.[32] Long-term treatment with SSRI induces desensitization/internalization of 5-HT autoreceptors, and this could lead to the downregulation of some postsynaptic receptors, such as the 5-HT_{2A} and 5-HT_{2C} subtypes. The end result of this process is thought to be a net activation of the 5-HT system.[32] Our results may partly arise from a net reduction of serotonin function by 5-HT autoreceptors produced by acute paroxetine administration.

We should briefly mention a relatively strong affinity of paroxetine for the norepinephrine transporter, $K_D = 40 \pm 2$ nmol[23] and muscarine receptor, $K_i = 72 \pm 3$ nmol/L,[22] but it is beyond the scope of the present study to examine the effects of paroxetine on these pathways.

In conclusion, paroxetine single acute administration diminished brain activity induced by motivation in healthy subjects. Our results may partially explain clinically observed decreased motivation seen in patients with relatively mild symptoms taking an initial paroxetine tablet dose of 10 or 20 mg for the first time. Further research is needed to clarify the effects of SSRI on brain activity with respect to cognitive and motor functions.

ACKNOWLEDGMENTS

We gratefully acknowledge the contributions of the members of the Tamagawa University Brain Science Institute. This work was supported by Grants-in-Aid for Scientific Research #19790838 and #18300275 for T. M. and Tamagawa University Global Center of Excellence (GCOE) program from the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT).

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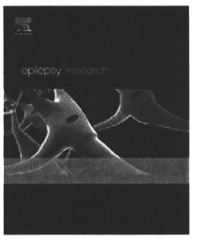

Abnormal mismatch negativity for pure-tone sounds in temporal lobe epilepsy

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Received 31 May 2010; received in revised form 8 January 2011; accepted 23 January 2011

KEYWORDS
Temporal lobe epilepsy (TLE);
Event-related potentials (ERPs);
Mismatch negativity (MMN);
Auditory processing;
Pre-attentive memory

Summary Auditory processing abnormalities in temporal lobe epilepsy (TLE) were assessed by investigating mismatch negativity (MMN) in a group of 20 TLE patients and 20 healthy control subjects. MMN is an event-related potential (ERP) component that reflects pre-attentive sensory memory function. A passive oddball paradigm using frequency changes in sinusoidal tones was employed to evoke MMN. MMN at frontocentral sites was enhanced in TLE patients relative to controls, while mismatch signals at mastoid sites (i.e., mismatch positivity; MMP) did not differ between the two groups. In the MMP temporal range, greater positivity at mastoid sites in response to standard stimuli was observed in TLE patients than in controls. Both MMN and MMP were significantly delayed in the TLE group. These findings demonstrate that TLE patients have impaired pre-attentive processing of pure-tone sounds. Enhanced frontocentral MMN may reflect hyperexcitability of the frontal lobes in compensation for dysfunction of the temporal lobes. Larger positivity at the mastoids in response to standard stimuli may be attributed to poor neuronal adaptation in the temporal lobe. Taken together, results suggest that evaluation of MMN/P is a useful physiological tool for identifying pre-attentive auditory memory dysfunction in TLE.

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doi:10.1016/j.eplepsyres.2011.01.009

Please cite this article in press as: Miyajima, M., et al., Abnormal mismatch negativity for pure-tone sounds in temporal lobe epilepsy. Epilepsy Res. (2011), doi:10.1016/j.eplepsyres.2011.01.009

Introduction

Temporal lobe epilepsy (TLE) is often associated with memory impairment due to damage in the hippocampus and surrounding structures (Dietl et al., 2008; McCagh et al., 2009). It has been repeatedly shown that both short-term and long-term memory are impaired in TLE (Butler and Zeman, 2008; McCagh et al., 2009). However, little is known concerning dysfunction in initial sensory memory encoding in TLE.

Mismatch negativity (MMN) is an early auditory event-related potential (ERP) elicited when infrequent (''deviant'') sounds occur in a sequence of repetitive (''standard'') sounds (Näätänen et al., 1978). It has been proposed that MMN automatically arises if there is mismatch between the physical features of a deviant stimulus and a neuronal sensory-memory trace produced by repetitive standard stimuli (Näätänen et al., 1989). MMN is believed to reflect the earliest cortical event in the cognitive processing of auditory information (Pfefferbaum et al., 1995) and thus to be a part of auditory pre-attentive memory (Cowan et al., 1993). MMN can be elicited even in the absence of attention, and effects of motivation are minimal (Näätänen, 2000). MMN has therefore received considerable interest because of its potential application to clinical research, and has been studied in various populations including newborns (Stefanics et al., 2009) and children (Milovanov et al., 2009) as well as in disorders such as schizophrenia (Kasai et al., 2002; Salisbury et al., 2007) and Alzheimer's disease (Pekkonen et al., 2001). Focusing on pre-attentive processes may be the only means of assessing cognitive function in patients with advanced cognitive decay who are unable to perform traditional cognitive tasks.

To date, the extant literature evaluating MMN response in epilepsy patients is limited and discrepant, with some studies pointing to attenuated or delayed MMN, whereas others report enhanced MMN. For example, Lin et al. (2007) investigated the magnetic equivalent of mismatch negativity (MMNm) in intractable TLE patients using magnetoencephalography (MEG). Longer MMNm latencies were observed in patients than in healthy controls. The authors also evaluated inter-trial phase coherence as indexed by phase-locking factors using wavelet-based analyses. For patients who became seizure-free after removal of right temporal epileptic foci, phase-locking in response to deviant stimuli was enhanced and more strongly distributed in frontotemporal regions. Such findings suggest that successful surgery may improve auditory change detection. Borghetti et al. (2007) demonstrated similar improvements in drug-resistant epilepsy patients who underwent vagus nerve stimulation (VNS). Prior to VNS implantation, MMN latencies in some patients were abnormally late and attenuated relative to controls. After implantation, however, these patients exhibited a major reduction in MMN latency and increase in amplitude, suggesting a positive effect of VNS on pre-attentive processes.

In the pediatric field, MMN has been shown to be absent or prolonged for speech (but not tones) in patients with benign childhood epilepsy with centro-temporal spikes (BCECTS) (Boatman et al., 2008; Duman et al., 2008). Patients with BCECTS with atypical features and learning difficulties have also been shown to exhibit attenuated MMN amplitudes (Metz-Lutz and Filippini, 2006). Furthermore, Honbolygó et al. (2006) found that in Landau–Kleffner syndrome, MMN was obtained for phoneme differences but was absent for stress pattern differences.

In contrast to findings of attenuated MMN amplitudes and delayed latencies, Usui et al. (2009) observed distinctively large N100m signals, the magnetic counterpart of N1/N100, in autosomal-dominant lateral temporal lobe epilepsy with seizures provoked by auditory stimuli. Similarly, Gene-Cos et al. (2005) reported that MMN amplitudes tended to be larger in patients with epilepsy than in healthy controls. Furthermore, work from our own laboratory has shown extremely large MMN amplitudes in response to high-frequency deviants in a patient with frontal lobe epilepsy with seizures provoked by high-frequency auditory stimuli (Miyajima et al., 2009). One could hypothesize that the higher amplitudes observed in epileptic patients indicate increased activation of the same neuronal population as in controls, or that extra neuronal circuits are activated in epileptic patients (Myatchin et al., 2009).

Taken together, the existing literature provides discrepant accounts of how MMN is affected in epilepsy patients. Furthermore, most studies in adult epileptics have not focused on patients with specific types of epileptic syndromes or epileptogenic regions. To this end, the broad aim of the current study was to better characterize potential differences in cortical activation patterns between TLE patients and controls during pre-attentive auditory processing. Specifically, we employed a passive oddball task and evaluated whether frontal and mastoid mismatch components were equally affected by TLE. If a single auditory cortex generator is responsible for any potential abnormalities in TLE, we hypothesized that similar MMN changes should be expected across electrode locations, given that frontal and mastoid electrodes are approximately equidistant from Heschl's gyrus (Baldeweg et al., 2002).

In addition to characterizing MMN differences between TLE patients and controls, a secondary objective was to investigate whether MMN abnormalities, if present in TLE patients, were associated with epileptic seizures. Specifically, we evaluated whether mismatch components differed between patients who experienced at least one seizure in the months leading up to the experiment and patients who were seizure-free during the same time period.

Methods

Subjects

Twenty TLE patients (8 females and 12 males; mean age 33.9 ± 10.0 (SD) years) and 20 comparable healthy control subjects (10 females and 10 males; mean age 34.0 ± 7.8 years) participated in this study as volunteers.

Epilepsy patients were recruited from Tokyo Medical and Dental University Hospital and Hara Clinic, a specialized epilepsy clinic certified as a training facility by The Japan Epilepsy Society. All patients had partial seizures with features strongly suggestive of a TLE diagnosis, including simple partial seizures characterized by autonomic and/or psychic symptoms, certain phenomena such as olfactory and auditory sensations, and complex partial seizures beginning with motor arrest followed by oroalimentary automatism

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Table 1 Clinical information for healthy controls and TLE patients.

Variables	Controls ($n=20$)			TLE patients ($n=20$)			
	Mean	(SD)	Range	Mean	(SD)	Range	
Age (years)	34.0	(7.8)	23–50	33.9	(10.0)	20–50	NS
Education (years)	16.6	(3.3)	12–22	14.5	(1.7)	12–16	NS
Gender (male/female)	10/10			12/8			
Duration of epilepsy (years)	NA			13.7	(9.8)	3–33	
Age of onset (years)	NA			20.1	(11.4)	0–45	
Side of epileptic focus (left/right/bilateral or undetermined)	NA			9/4/7			
Seizure status (intractable/remission)	NA			12/8			
Number of AED	NA			1.8	(1.0)	1–4	

AED, antiepileptic drug; NA, not applicable; NS, no significant difference.

(Commission on Classification and Terminology of the International League Against Epilepsy, 1989). Diagnoses were based on a combination of clinical symptoms, EEG, and structural/functional imaging data. Exclusion criteria for both groups included comorbid psychiatric disease, substance abuse or dependence, and reports of hearing or vision problems at the time of the experiment. Additional exclusion criteria for the control group included a history of psychiatric disease, history of traumatic brain injury with any known cognitive consequences or loss of consciousness, history of convulsions other than simple febrile seizures, and psychiatric disease or epileptic disorder in first-degree relatives.

Table 1 summarizes the subjects' clinical characteristics. Patients were divided into two subgroups, an intractable subgroup and a remission subgroup. The intractable subgroup experienced at least one seizure within a 20-month period prior to the experiment, while the remission subgroup was completely seizure-free during this time. All patients were treated with at least one anti-epileptic drug (AED), e.g., carbamazepine or phenytoin, for seizure control.

The study was approved by the Ethics Committee at Tokyo Medical and Dental University. Written informed consent was obtained from each participant after thoroughly describing the experiment.

Procedure

Subjects were presented with auditory stimulus sequences consisting of 600 standard stimuli and 150 deviant stimuli delivered in random order. Fifty deviant stimuli were presented to each subject in a single block, and each subject completed three blocks. The experimental conditions were designed to elicit MMN in response to changes in frequency of pure tones. To this end, stimuli consisted of pure tones presented for 100 ms each, with a rise/fall time of 5 ms and a stimulus onset asynchrony (SOA) of 500 ms. Standard stimuli (1000 Hz) comprised 80% of all trials, while deviant stimuli (1050 Hz) comprised 20%. The standard pure tone frequency of 1000 Hz is commonly used in psychoacoustic and electrophysiological studies, and was chosen because it does not directly correspond to the fundamental of any musical note. Stimuli were delivered binaurally via earphones at 90 dB as subjects watched a silent film while seated and were instructed to ignore auditory stimuli.

ERP recording

EEG was recorded using a portable bio-amplifier recording device (Polymate AP-1532 with silver/silver chloride electrodes, or Polymate AP-216 with active electrodes, TEAC Corporation, Japan) from the midline (Fz, Cz, Pz, and Oz) and bilateral mastoids. The tip of the nose served as the reference for all electrodes. Two electrodes were placed above the left eye and below the right eye to monitor the electrooculogram (EOG). Impedance between the electrodes and skin did not exceed 5 kΩ. The sampling rate was 1000 Hz for each channel and the recording bandwidth was between 0.05 Hz and 300 Hz.

Data analysis

Data analysis focused on a 600 ms time window ranging from 100 ms pre-stimulus to 500 ms post-stimulus onset. The pre-stimulus baseline was corrected separately for each channel according to the mean EEG amplitude over the 100 ms period. Averaging and artifact rejection were performed off-line. Trials with excessive movement activity or with EOG activity exceeding 100 μV peak-to-peak were excluded from analysis. Average waveforms were obtained separately for deviant and standard stimuli, with a minimum of 100 deviant trials for each subject.

Because MMN is known to show inverted polarity at mastoid locations, the term 'mismatch positivity' (MMP) has been adopted to describe the mismatch component at this location (Baldeweg et al., 1999). For this reason, we use the term MMP when describing mastoid findings, and MMN for findings at all other electrode locations.

Statistical analyses

The mean amplitudes of standard and deviant waveforms were defined as the average amplitude for each waveform 100–250 ms post-stimulus onset (the range in which MMN/P is typically found). MMN/P peak latency was defined as the latency of the peak showing maximal negativity/positivity 100–250 ms post-stimulus onset for the deviant – standard difference waveform.

Mean amplitudes for standard and deviant waveforms were first analyzed using three-way repeated-measures analyses of variance (ANOVA), with separate ANOVAs conducted for sites with negative and positive polarity. For both ANOVAs, factors included the between-subjects factor GROUP (TLE and control), and two within-subject factors STIMULUS (standard and deviant) and SITE (for sites with negative polarity: Fz and Cz; for sites with positive polarity: left and right mastoid). Additional two-way ANOVAs with one between-subject factor GROUP (TLE and control), and one within-subject factor SITE (for sites with negative polarity: Fz and Cz; for sites with positive polarity: left and right mastoid) followed separately for standard and deviant waveforms.

MMN/P peak latencies based on the difference waveform were examined using two-way repeated-measures ANOVAs with one between-subject factor GROUP (TLE and control), and one within-

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Table 2 Mean amplitudes of standard, deviant and difference (MMN) waveforms as well as MMN peak latencies in controls and TLE patients.

Variables	Site		Controls ($n=20$)		TLE patients ($n=20$)	
			Mean	(SD)	Mean	(SD)
Mean amplitude (μV)						
Standard	Frontocentral	Fz	0.17	(0.70)	0.17	(1.31)
		Cz	0.15	(0.69)	0.07	(1.12)
	Mastoid	L	−0.22	(0.66)	0.43	(0.56)
		R	−0.31	(0.67)	0.42	(0.59)
Deviant	Frontocentral	Fz	0.11	(0.73)	−0.56	(1.59)
		Cz	0.24	(1.07)	−0.55	(1.39)
	Mastoid	L	0.13	(0.60)	0.49	(0.98)
		R	0.16	(0.56)	0.45	(1.20)
MMN	Frontocentral	Fz	−0.05	(0.73)	−0.75	(0.84)
		Cz	−0.10	(1.19)	−0.64	(0.93)
	Mastoid	L	0.35	(0.51)	0.06	(0.91)
		R	0.47	(0.58)	0.02	(0.63)
Peak latency (ms)						
MMN	Frontocentral	Fz	133	(28)	179	(36)
		Cz	141	(42)	171	(41)
	Mastoid	L	145	(31)	157	(53)
		R	150	(33)	185	(39)

subject factor SITE (for sites with negative polarity: Fz and Cz; for sites with positive polarity: left and right mastoid).

Finally, to explore whether potential abnormalities in TLE patients were associated with epileptic seizures, the TLE group was divided into two subgroups, an intractable subgroup and a remission subgroup. Mean amplitudes for standard and deviant waveforms were first analyzed using three-way ANOVAs with one between-subjects factor SUBGROUP (intractable and remission), and two within-subject factors STIMULUS (standard and deviant) and SITE (for sites with negative polarity: Fz and Cz; for sites with positive polarity: left and right mastoid). When a three-way ANOVA yielded a significant interaction or trend for an interaction between factors, a two-way ANOVA was performed for the relevant factors. MMN/P peak latencies based on the difference waveform were examined using two-way repeated-measures ANOVAs with one between-subjects factor SUBGROUP (intractable and remission), and one within-subject factor SITE (for sites with negative polarity: Fz and Cz; for sites with positive polarity: left and right mastoid).

With respect to all analyses, statistics for sites showing a negative mismatch component were limited to Fz and Cz because MMN typically is largest at midline frontocentral sites. As anticipated, visual inspection of difference waveforms at Pz and Oz revealed small and obscure mismatch signals such that it was difficult to determine individual peaks. MMN typically reverses polarity at nose-referenced mastoid sites. To this end, evaluation of waveforms at mastoid sites enabled comparison of polarity with waveforms at Fz and Cz, providing additional assurance that the observed negativity at these sites was a "true" mismatch response (Näätänen et al., 2007).

Results

Fig. 1 presents grand-averaged ERP waveforms for standard and deviant stimuli in TLE patients and controls at Fz, Cz, and left and right mastoids, with associated mean amplitudes presented in Table 2. Although statistical analyses

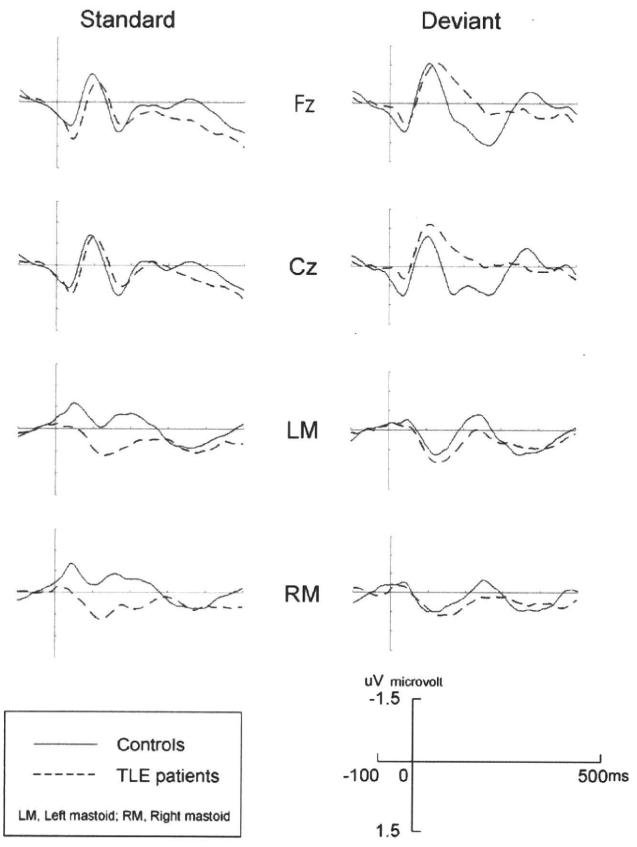

Figure 1 Comparison between grand-averaged ERPs for standard and deviant stimuli in controls and TLE patients. Solid line, control group; striped line, epilepsy group.

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Table 3 Mean amplitudes of standard deviant and difference (MMN) waveforms as well as MMN peak latencies in TLE intractable and remission subgroups.

Variables	Site		Intractable (n = 12)		Remission (n = 8)	
			Mean	(SD)	Mean	(SD)
Mean amplitude (μV)						
Standard	Frontocentral	Fz	0.23	(0.64)	0.08	(0.61)
		Cz	0.12	(1.46)	−0.01	(0.53)
	Mastoid	L	0.45	(0.68)	0.40	(0.36)
		R	0.43	(0.70)	0.43	(0.39)
Deviant	Frontocentral	Fz	−0.60	(1.91)	−0.51	(1.06)
		Cz	−0.66	(1.50)	−0.38	(1.29)
	Mastoid	L	0.36	(1.09)	0.70	(0.82)
		R	0.36	(1.06)	0.57	(0.53)
MMN	Frontocentral	Fz	−0.82	(0.84)	−0.63	(0.87)
		Cz	−0.78	(0.85)	−0.38	(1.03)
	Mastoid	L	−0.10	(0.96)	0.09	(0.90)
		R	−0.06	(0.73)	0.02	(0.58)
Peak latency (ms)						
MMN	Frontocentral	Fz	183	(34)	149	(72)
		Cz	172	(43)	148	(73)
	Mastoid	L	165	(64)	126	(59)
		R	193	(45)	147	(64)

for mean amplitude were performed based upon standard and deviant waveforms, we also present grand-averaged MMN/P waveforms (i.e., difference waveforms) in Fig. 2 for ease of comparing mismatch signals across groups. For the same reason, MMN/P mean amplitudes also are presented in Table 2, with mean amplitude defined as the average amplitude of the deviant − standard difference waveform 100–250 ms post-stimulus onset. Peak latencies for the difference waveform are also reported in Table 2. Finally, Table 3 presents data relevant to the TLE subgroup analysis, including mean amplitudes of standard, deviant and difference (MMN/P) waveforms, as well as peak latencies of the MMN/P waveform.

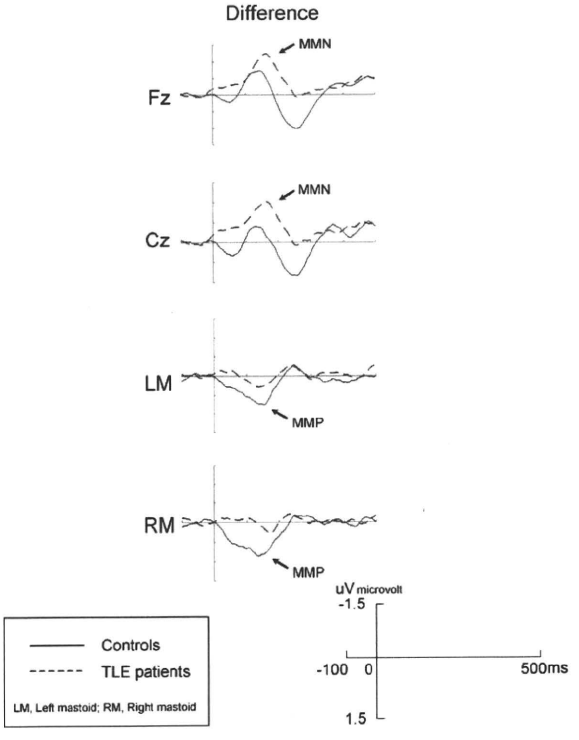

Figure 2 Deviant minus standard difference waveforms in controls and TLE patients. Solid line, control group; striped line, epilepsy group.

Frontocentral sites

A 2 (GROUP: TLE vs. control) × 2 (STIMULUS: standard vs. deviant) × 2 (SITE: Fz vs. Cz) repeated-measures ANOVA examining mean amplitudes for standard and deviant stimuli in the range of 100–250 ms revealed a significant main effect of STIMULUS [$F(1, 38) = 5.05$, $p < 0.05$], such that deviant amplitudes were greater than standard amplitudes. A significant interaction between STIMULUS and GROUP was also found [$F(1, 38) = 5.74$, $p < 0.05$], indicating that the difference between deviant and standard amplitudes in TLE patients was greater than that in controls. Stated another way, MMN was enhanced in TLE patients relative to controls (see Figs. 1 and 2 and Table 2). Separate 2 (SITE: Fz vs. Cz) × 2 (GROUP: TLE vs. control) repeated-measures ANOVAs for deviant and standard mean amplitudes showed no significant main effects or interactions. Additionally, visual inspection of waveforms revealed that deviant waveforms in TLE patients were still negative at a latency of 200 ms, whereas in controls deviant waveforms shifted from negative to positive around 150 ms, effectively leading to prolonged MMN duration in TLE patients (see Fig. 1 and Table 2).

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With respect to MMN peak latency (based on the deviant – standard difference waveform), a two-way repeated measures ANOVA revealed a significant main effect of GROUP [$F(1, 38) = 12.45$, $p < 0.01$], such that MMN peak latency was delayed in patients compared with controls. No significant main effect of SITE or interaction between GROUP and SITE was observed.

Mastoid sites

A three-way repeated-measures ANOVA examining mean amplitudes for standard and deviant stimuli revealed significant main effects of both GROUP [$F(1, 38) = 7.14$, $p < 0.05$] and STIMULUS [$F(1, 38) = 5.08$, $p < 0.05$]. Collapsed across stimulus type and site, mean amplitudes were greater in TLE patients than controls; collapsed across group and site, deviant amplitudes were greater than standard amplitudes. No significant interaction between factors was observed. In addition, separate two-way repeated-measures ANOVAs were performed for deviant and standard mean amplitudes. No significant main effects of GROUP or SITE or an interaction between factors were found for deviant stimuli. Conversely, for standard stimuli a main effect of GROUP was found [$F(1, 38) = 13.65$, $p < 0.001$], with TLE patients showing greater mean amplitudes than controls (see Fig. 1 and Table 2). No main effect of SITE or an interaction between GROUP and SITE was found for standard stimuli.

A two-way repeated measures ANOVA for MMP peak latency based on the difference waveform revealed a significant main effect of GROUP ($F(1, 38) = 4.39$, $p < 0.05$) and SITE ($F(1, 38) = 7.65$, $p < 0.01$), indicating that MMP peak latency was delayed in TLE patients relative to controls, and that both groups displayed delayed MMP peak latencies in the right relative to left mastoid (see Fig. 2 and Table 2). There was a trend toward a significant interaction between GROUP and SITE [$F(1, 38) = 3.88$, $p = 0.056$], although the difference did not reach a significant level.

MMN/P and epileptic seizures

At frontocentral sites, a 2 (STIMULUS: standard vs. deviant) × 2 (SITE: Fz vs. Cz) × 2 (SUBGROUP: intractable vs. remission) repeated-measures ANOVA for mean amplitudes of standard and deviant waveforms in the range of 100–250 ms revealed a significant main effect of STIMULUS [$F(1, 38) = 9.44$, $p < 0.01$], such that deviant amplitudes were greater than standard amplitudes (see Table 3). No main effect of GROUP or interaction between STIMULUS and SUBGROUP was observed. For MMN peak latency, a 2 (SITE: Fz vs. Cz) × 2 (SUBGROUP: intractable vs. remission) repeated measures ANOVA revealed no significant main effects or interactions.

At mastoid sites, a three-way repeated measures ANOVA for mean amplitudes of standard and deviant stimuli revealed no significant main effects or interactions between factors. With respect to MMP peak latency, a two-way repeated measures ANOVA revealed a significant main effect of SITE [$F(1, 18) = 7.06$, $p < 0.05$], reflecting longer latencies in both groups for right than left mastoid (see Table 3). No main effect of SUBGROUP or interaction between SITE and SUBGROUP was observed.

Discussion

In response to a passive auditory oddball task, patients with TLE exhibited patterns of cortical activity that differed from control subjects in several ways. First, at frontocentral sites, MMN was enhanced in TLE patients relative to controls, as revealed by a significant GROUP by STIMULUS interaction for mean amplitude. Secondly, at mastoid sites, TLE patients showed greater standard waveform amplitudes than controls. Finally, in addition to amplitude differences between groups, analyses revealed longer MMN/P peak latencies in TLE patients relative to controls at both frontocentral and mastoid sites.

A number of researchers have noted that mismatch potentials recorded from mastoid electrodes may exhibit characteristics different from those of MMN recorded from frontal electrodes (Baldeweg et al., 2002; Sato et al., 2002). Early studies of MMN identified a single dipole generator within the bilateral superior temporal gyri (STG) in the vicinity of Heschl's gyri (Scherg et al., 1989). Toward the mastoids, an inversion of polarity is typically observed and has been considered evidence for the generation of MMN in the temporal lobe (Sams et al., 1985). However, more recently it has been suggested that the single dipole model may not account for all the data, and that more than one source may contribute to the scalp MMN (Giard et al., 1994). To this end, multichannel MEG and EEG studies (Rinne et al., 2000) as well as intracranial recordings (Rosburg et al., 2005) have identified additional generators in the frontal cortex. In the latter study, MMN was observed in two patients at electrode contacts over lateral inferior frontal cortex and in one patient in a frontal interhemispheric electrode strip, providing evidence for the participation of frontal gyri in MMN generation. Recent observations have led to the view that temporal electrodes mainly detect mismatch sources in the superior temporal lobe, including perhaps its lateral surface, while electrodes over the frontal scalp may detect signals from putative frontal generators (Escera et al., 2003; Näätänen et al., 2007).

In addition to debate surrounding the number of MMN generators, the specific neural mechanisms underlying MMN generation also remain controversial. Two major competing hypotheses, the model adjustment hypothesis and the adaptation hypothesis, are considered below in relation to the current findings.

To date, the most commonly suggested mechanism underlying MMN generation is a pre-attentive sensory memory mechanism (Tiitinen et al., 1994) posited to automatically compare present auditory input and memory traces of previous sounds (Näätänen et al., 2007). More specifically, it has been suggested that MMN may reflect on-line modifications of a perceptual model that is updated when auditory input does not match its predictions (Näätänen and Winkler, 1999), a hypothesis known as the model-adjustment hypothesis. Based on this model, MMN is thought to result from two underlying functional processes: a sensory memory mechanism arising from temporal generators and an automatic attention-switching process arising from frontal generators (Giard et al., 1990). Providing support for this model, Escera et al. (2003) demonstrated evidence for prefrontal cortex involvement in providing top-down modulation of a deviance detection system in the temporal cortex. With respect to

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the current study, findings of enhanced MMN at frontocentral sites in TLE patients might thus be interpreted as frontal lobe hyperexcitability to compensate for temporal lobe dysfunction. That is, a larger number of synchronously activated frontal neurons may be required for successful automatic attention-switching in TLE patients than in controls, due to impairment of a initial sensory memory mechanism in the temporal lobe.

An alternative mechanism recently proposed by Jääskeläinen et al. (2004) suggests that MMN results from a much simpler mechanism of local neuronal adaptation in the auditory cortex. According to the adaptation hypothesis, reduced responsiveness in the auditory cortex during continuous stimulation is sufficient to explain the generation of an apparent MMN. In the current study, although deviant – standard differences (i.e., MMP) at mastoid sites did not significantly differ between the two groups, greater standard waveform amplitudes were observed in patients than in controls. With respect to the adaptation hypothesis, such findings may reflect poor neuronal adaptation in the temporal lobe such that repeated presentation of standard stimuli does not lead to reduced responses. In other words, processing resources may continue to be allocated in TLE patients despite the repetitive nature of the standard stimuli (Myatchin et al., 2009). TLE may be characterized by excitability of the temporal lobe despite stimulus repetition, which might be related to epileptogenesis of the temporal cortex. The current results suggest that adaptation mechanism of the temporal cortex for stimuli that are subsequently repeated may be impaired in TLE.

It also bears noting that longer latency components such as P3a may have affected the pre-stimulus baseline period, in turn affecting MMN/P amplitudes given that epochs were baseline-corrected. Specifically, because we chose a short SOA (500 ms), standard trials preceded by a deviant trial may have had different pre-stimulus baseline periods than those preceded by another standard trial. Although P300 abnormalities in TLE are controversial, studies in chronic TLE patients typically report trends toward lower P300 amplitudes relative to controls (e.g., Drake et al., 1986; Tuunainen et al., 1995; Abubakr and Wambacq, 2003). To avoid potential confounds related to P3a, future studies should exclude standard trials preceded by deviant trials from averaging.

In addition to amplitude differences between TLE patients and controls, a second key difference was an increase in MMN/P latency in TLE patients, consistent with previous reports (Lin et al., 2007; though see Duncan et al., 2009, for reports of normal auditory P300 latencies in patients with complex partial seizures). Because ERPs provide a chronological measure of brain function and ERP latencies are thought to indicate timing of covert neuronal events in which certain subroutines in the brain are activated (Kok, 1997), increased MMN/P latencies in TLE patients in the current study may be the result of an early but not later slowing in auditory information processing speed.

Furthermore, in TLE patients the MMN component persisted longer at frontocentral sites than in controls, consistent with previous findings by Gene-Cos et al. (2005). The authors argue that prolonged MMN duration might point to difficulty mainly in ''the closure mechanism of the MMN process''. They suggest that this information processing dysfunction could be related to concentration and memory difficulties observed in TLE patients, given that patients may spend more time evaluating stimulus novelty than controls and may experience difficulty switching attention from one stimulus to another difficult (Piazzini et al., 2006). Such findings in epilepsy patients are in agreement with previous studies in which barely discriminable tones elicited delayed MMN peaks (Näätänen and Alho, 1995; Inouchi et al., 2004) with delays increasing as the magnitude of deviation decreased (Yabe et al., 2001; Inouchi et al., 2004).

Interestingly, collapsed across subject groups, MMP was delayed in the right mastoid compared with the left. Because of the small number of patients whose epileptic focus was clearly lateralized, statistical analyses could not be conducted to evaluate the relationship between MMP latency and laterality of epileptic focus. Furthermore, given that laterality effects have not been reported previously with respect to MMP latency in healthy adults, further investigation is warranted before drawing strong conclusions about this finding.

Finally, our patient subgroup analysis investigating the relationship between seizures and MMN/P did not reveal any significant differences between groups, suggesting that the occurrence or absence of seizures in the months leading up to the experiment did not significantly affect MMN/P.

Because all patients were being treated with AEDs at the time of data collection, it bears noting that use of AEDs may have affected MMN/P amplitudes and latencies. It has been shown, for example, that anti-epileptic medication can have an effect on motor reaction times and on latencies in ERP studies (Lagae, 2006; Myatchin et al., 2009), as well as an overall dampening effect on amplitudes (Rosburg et al., 2005). Benzodiazepines, which are also used as AEDs, have been found to reduce MMN amplitude (Rosburg et al., 2004). To this end, the current finding of enhanced MMN amplitudes in TLE patients cannot be explained as a simple dampening effect of AEDs, though further studies will be required to better address the effects of AEDs on MMN. Finally, although all patients reported normal hearing levels, it is possible that MMN/P was affected by subclinical differences in auditory discriminative abilities between patients and controls.

Taken together, results from the present study reveal clear cortical abnormalities in TLE patients that have not been well-characterized previously by conventional EEG. In TLE patients, enhanced MMN at frontocentral sites and greater positivity at mastoid sites of standard waveforms may be interpreted in terms of increased activation of the same neuronal population as in controls, or activation of extra neuronal circuits. In conclusion, the current study extends previous findings of impaired short and long-term memory in TLE patients (Butler and Zeman, 2008; McCagh et al., 2009) by revealing that initial sensory memory is impaired in TLE as well. Our findings indicate that MMN/P can be useful as a physiological probe of pre-attentitve sensory memory for tones in TLE.

Acknowledgements

We appreciate the advice and expertise of Dr. Hiroshi Otsubo and Dr. Tomoyuki Akiyama. We are also grateful to Dr. Kikuo

Please cite this article in press as: Miyajima, M., et al., Abnormal mismatch negativity for pure-tone sounds in temporal lobe epilepsy. Epilepsy Res. (2011), doi:10.1016/j.eplepsyres.2011.01.009

Ohno, Dr. Motoki Inaji, Atsushi Shirasawa, Michi Baba, Yasuka Emori, Ayasa Matsuda, Mina Yamada, and the staff at Hara Clinic for their help and assistance.

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Please cite this article in press as: Miyajima, M., et al., Abnormal mismatch negativity for pure-tone sounds in temporal lobe epilepsy. Epilepsy Res. (2011), doi:10.1016/j.eplepsyres.2011.01.009

SOCIAL NEUROSCIENCE, 2010, 5 (1), 19–29

Psychology Press
Taylor & Francis Group

Acquired personality traits of autism following damage to the medial prefrontal cortex

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Recent neuroimaging studies on "theory of mind" have demonstrated that the medial prefrontal cortex (PFC) is involved when subjects are engaged in various kinds of mentalising tasks. Although a large number of neuroimaging studies have been published, a relatively small amount of neuropsychological evidence supports involvement of the medial PFC in theory of mind reasoning. We recruited two neurological cases with damage to the medial PFC and initially performed the standard neuropsychological assessments for intelligence, memory, and executive functions. To examine theory of mind performance in these two cases, four kinds of standard and advanced tests for theory of mind were used, including first- and second-order false belief tests, the strange stories test, and the faux pas recognition test. Both patients were also requested to complete the questionnaire for the autism-spectrum quotient. Neither case showed impairment on standard theory of mind tests and only mild impairments were seen on advanced theory of mind tests. This pattern of results is basically consistent with previous studies. The most interesting finding was that both cases showed personality changes after surgical operations, leading to characteristics of autism showing a lack of social interaction in everyday life. We discuss herein the possible roles of the medial PFC and emphasize the importance of using multiple approaches to understand the mechanisms of theory of mind and medial prefrontal functions.

Keywords: Theory of mind; Mentalising; Autism-spectrum quotient; Medial prefrontal cortex; Anterior cingulate cortex.

INTRODUCTION

Recent studies in social neuroscience have focused on the neural bases of cognitive processes for understanding other minds. A number of neuroimaging studies of "theory of mind" have demonstrated that the medial prefrontal cortex (PFC) or anterior cingulate (paracingulate) cortex is involved in various kinds of tasks requiring mentalising functions (Brunet, Sarfati, Hardy-Baylé, & Decety, 2000; Castelli, Happé, Frith, & Frith, 2000; Gallagher & Frith, 2003; Gallagher et al., 2000; Vogeley et al., 2001). This area has been recognized as one of the "social brain" areas, together with areas such as the superior temporal sulcus, amygdala, insula, posterior

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This study was supported by Grant-in-Aids for Scientific Research (16203038) from the Japan Society for the Promotion of Science (JSPS). We are grateful to the two patients who participated in this study.

www.psypress.com/socialneuroscience
DOI:10.1080/17470910902990584

cingulate (retrosplenial cortex), and fusiform gyrus (Brüne, Ribbert, & Schiefenhövel, 2003; Wheatley et al., 2007). Although previous studies have shown that these areas play different roles in self-related processing, the medial PFC has been identified as one of the cortical midline structures subserving self-related processings such as monitoring, self-awareness, agency, and autobiographical memory (for review, see Northoff & Bermpohl, 2004). Among all these areas, the medial PFC has been considered essential for understanding mental states of self and others in social situations.

Another neuroscientific approach to theory of mind involves neuropsychological investigations to examine the performance of brain-damaged cases. The initial study by Happé, Brownell, and Winner (1999) reported that following right hemisphere damage, cases showed impaired understanding of materials requiring attribution of mental states. Several other studies examining the effects of brain lesions on theory of mind performance have reported that focal frontal lesions impair the ability to infer mental states of others (Bach, Happé, Fleminger, & Powell, 2000; Happé, Malhi, & Checkley, 2001; Shamay-Tsoory, Tomer, Berger, & Aharon-Peretz, 2003; Stuss, Gallup, & Alexander, 2001). More careful examinations to understand the roles of different areas within the frontal lobe have indicated that right ventromedial prefrontal lesions impair detection of deception (Stuss et al., 2001) and empathy processing (Shamay-Tsoory et al., 2003), whereas lesions in the internal capsule impair advanced theory of mind performance for understanding the thoughts and feelings of fictional characters (Happé et al., 2001). Conversely, other studies have suggested that the ability to understand mental states was found to be intact in cases with orbitofrontal lesions (Bach et al., 2000).

Another comprehensive neuropsychological study of over 30 cases with unilateral (right or left) frontal lobe lesions found that both groups exhibited impaired performance on first- and second-order false belief tests (Rowe, Bullock, Polkey, & Morris, 2001). Stone, Baron-Cohen, & Knight (1998) tested performance on first- and second-order false belief tests and the faux pas recognition test in cases with orbitofrontal damage, and found that bilateral orbitofrontal lesions resulted in difficulty only in the ability to recognize a faux pas. Although these studies focused on the effects of damage to the frontal lobe, it remains unclear whether selective damage to the medial PFC yields any impaired performance on various kinds of theory of mind tests.

Some previous studies have actually examined the performance of cases with selective damage to the medial PFC. Baird et al. (2006) tested two cases and reported intact intellectual, memory, and language abilities, and visuoperceptual functions, but weak or impaired performance on selective executive function tests. No theory of mind performance was tested in that study. Another neuropsychological study addressed the question of theory of mind impairment by testing a case with a selective lesion in the medial PFC (Bird, Castelli, Malik, Frith, & Husain, 2004). They carefully examined performance of the patient on various kinds of theory of mind tests, but found no significant impairment on tests, and thus stated that extensive medial frontal regions are not necessary for theory of mind performance. The findings from both studies have some important implications for our understanding of the effects of damage to the medial PFC. Most interesting was the finding that following the damage to this area, cases did not show any severe impairment on test performance, including theory of mind performance. However, the data are currently too limited to reach solid conclusions on the effects of medial prefrontal damage.

Another unresolved question is concerned with personality changes in cases. In the classic case of Phineas Gage, damage to the orbitofrontal cortex resulted in severe behavioral disturbances in everyday life (Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994; Harlow, 1848). A number of previous studies have reported that cases with damage to the orbitofrontal cortex show severe sociopathic personality change (Eslinger & Damasio, 1985; Saver & Damasio, 1991). However, the question of whether cases with lesions involving the medial PFC, located in the vicinity of the orbitofrontal cortex, show any personality change remains unanswered. A recent meta-analysis of 39 functional imaging studies for autism-spectrum disorders indicated that the medial PFC was less activated during social task performance (e.g., theory of mind tests) in autism-spectrum disorders compared to neurotypical controls (Di Martino et al., 2009). Cases with damage to the medial PFC may show personality changes, leading to characteristics of autism.

Although previous neuropsychological studies of cases with damage to the medial PFC have shed light on the functions of this area, the

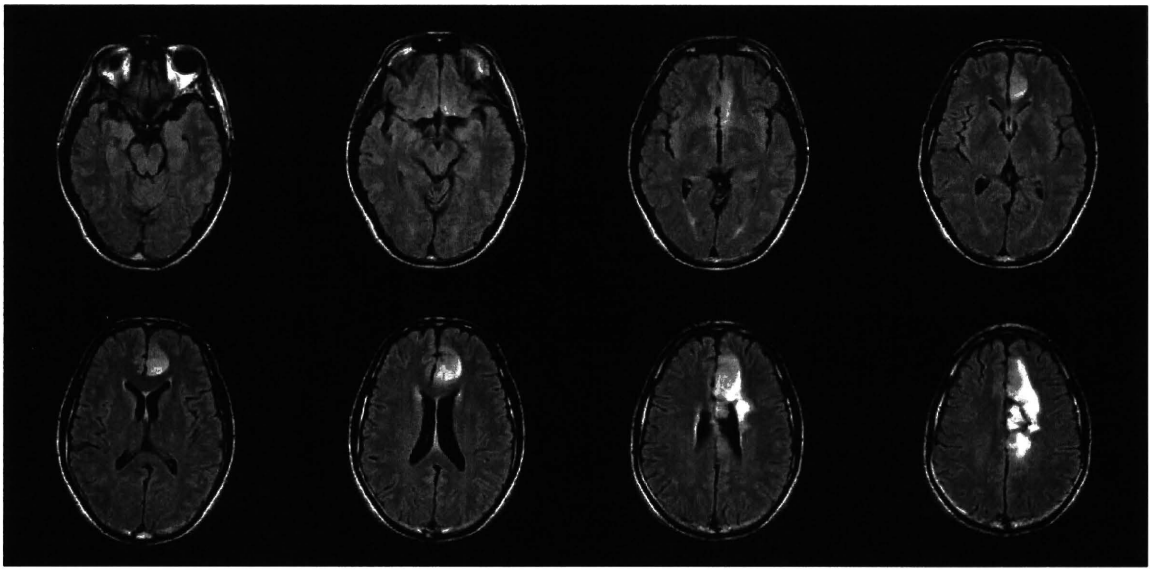

Figure 1. Transverse MRI with FLAIR acquisition of TO's brain. Left sides of images correspond to right side of the brain.

number of studies remains limited and actual effects on social functions following damage to this area remain poorly understood (Gallagher & Frith, 2003). We present herein two cases with damage to the medial PFC and report on their performance on various kinds of theory of mind tests, whether personality changes were evident, and behavioral disturbances in daily activities.

METHODS

Profiles of cases with medial prefrontal damage

We tested two individuals, TO and HC, with damage to the medial PFC. The first case, TO, was a 31-year-old man. A full-time employee of a big electronics company in Japan, he had undergone neurosurgery for brain tumor. Magnetic resonance imaging (MRI) with FLAIR (fluid attenuated inversion recovery) acquisition revealed that damage extended through the left-dominant medial prefrontal and anterior cingulate cortices, reaching the left supplementary motor area (Figure 1). The right hand and leg were moderately paralyzed for a few months after surgery, but those symptoms later resolved.

The most striking aspect on TO was a reported change in personality. According to his self-report, he noticed that his sense of reality was attenuated after surgery, leading him to feel detached from the world despite being sure of his location, and this feeling often occurred in a manner similar to a panic attack. These symptoms partly resembled the characteristics of depersonalization. He also mentioned that surgery had made him feel depressed, anxious and withdrawn from everything.

The second case, HC, was a 56-year-old man. An employer of a small private company in Japan, he had undergone surgery following rupture of a right pericallosal artery aneurysm. MRI with T1-weighted spin-echo acquisition revealed that the area of damage included the right-dominant medial prefrontal and anterior cingulate cortices, extending slightly into the right supplementary motor area (Figure 2).

According to self-reports, he noticed that his memory had deteriorated after surgery, with a feeling that most daily episodes could not be clearly remembered. He reported difficulty doing two things simultaneously, and became aware that everything needed a strong effort to be done. He also mentioned that his personality had changed after surgery, leading him to notice that feelings of sadness and anger had been dimmed and that he had become much more depressive, anxious and withdrawn compared to his previous personality.

Neuropsychological assessment

Three months after surgery, six of the more frequently used neuropsychological assessments

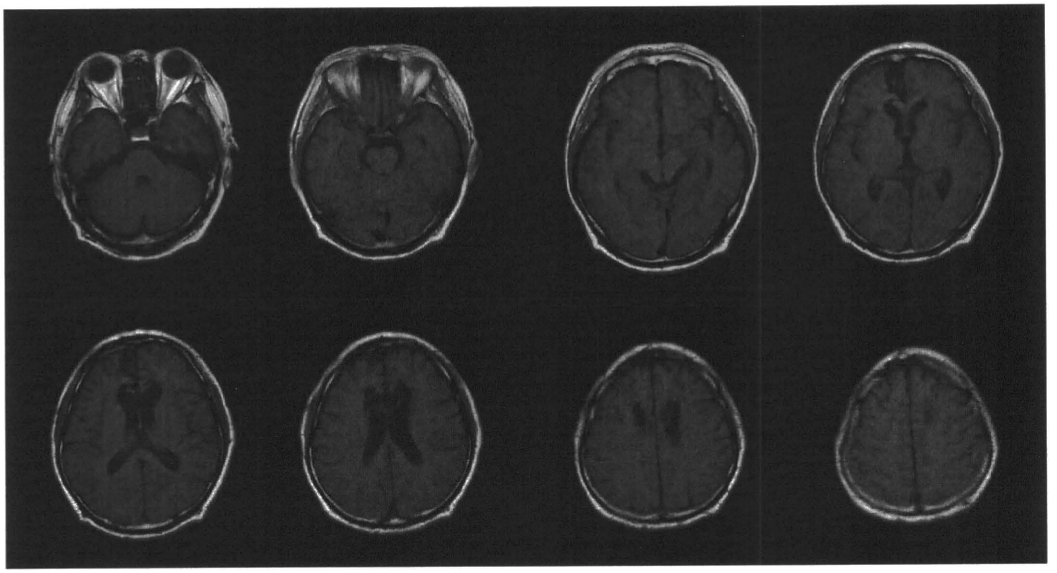

Figure 2. Transverse MRI with T1-weighted spin-echo acquisition of HC's brain. Left sides of images correspond to right side of the brain.

were conducted to examine higher-order cognitive functions in these cases. We selected: (1) Wechsler Adult Intelligence Scale–Revised (WAIS-R) for general intelligence, (2) Wechsler Memory Scale–Revised (WMS-R) for memory and attention, (3) Rey Auditory-Verbal Learning Test (RAVLT) for verbal recall ability, (4) Rey-Osterrieth Complex Figure Test (ROCFT) for visuoconstructive skills and visual memory, (5) Wisconsin Card Sorting Test (WCST) for abstract reasoning and ability to appropriately shift cognitive strategies, and (6) Stroop Test for selective attention and inhibition. The results of neuropsychological assessments in both cases are shown in Table 1.

TO's score on the intelligence test showed dissociation between verbal and performance intelligence quotient (IQ), with an inferior score on performance IQ. In the IQ test, he showed difficulty in performing subtests of block design, object assembly and digit symbols.

In terms of memory performance, TO showed lower scores on some measures for identifying delayed recall performance (e.g., delayed recall on WMS-R, RAVLT, and ROCFT) as compared to his relatively higher scores on other measures. The results of mild amnesia were consistent with his self-report regarding daily activities. For instance, he reported often becoming confused in remembering whether he has taken his medication.

TABLE 1
Neuropsychological assessments of TO and HC

Test	*TO*	*HC*
Intelligence		
Wechsler Adult Intelligence Scale–Revised (WAIS-R)		
Full scale IQ	88	91
Verbal IQ	101	92
Performance IQ	76	92
Memory		
Wechsler Memory Scale–Revised (WMS-R)		
Verbal memory	94	90
Visual memory	87	99
General memory	90	92
Attention and concentration	88	94
Delayed recall	65	100
Rey Auditory-Verbal Learning Test (RAVLT)		
Immediate recall, trials 1–5	6–9–9–10–11/15	3–7–10–9–11/15
Delayed recall	5/15	7/15
Delayed recognition	11/15	14/15
Rey-Osterrieth Complex Figure Test (ROCFT)		
Immediate recall	35/36	36/36
Delayed recall	4/36	22/36
Executive function		
WCST (Wisconsin Card Sorting Test)		
Categories achieved	4	5
Total perseverative errors	1	0
Stroop Test		
24 non-interference colour naming (errors)	14s (0)	22s (0)
24 interference colour naming (errors)	26s (1)	29s (1)

TO's performances on tests for executive function were all within normal range. Performance on the standardized aphasic test did not show any difficulties in language activities.

The second case, HC, showed an intellectual performance within normal range. In terms of memory performance, he exhibited normal scores on WMS-R, although scores on RAVLT and ROCFT were somewhat lower. In fact, in terms of daily activities, he showed difficulty with temporal-order judgments for everyday episodes within a time range of a few days.

HC's performance on tests for executive function was also within normal range. Performance on the standardized aphasic test did not show any difficulties in language activities.

Experimental investigations

We tested the two cases using four types of story comprehension task to clarify theory of mind performance. These included: (1) first-order false belief test (Baron-Cohen, Leslie, & Frith, 1985; Frith & Frith, 1999), (2) second-order false belief test (Baron-Cohen, 1989), (3) strange stories test (Happé, 1994), (4) faux pas recognition test (Baron-Cohen, O'Riordan, Stone, Jones, & Plaisted, 1999). The first-order false belief test is one of the most famous tests for theory of mind reasoning. This test assesses the ability to recognize that others can have false beliefs about the world that can differ from reality, and that people's behaviors can be predicted by the representation of others' mental states. The more complex second-order false belief test requires participants to understand a second person's concerns about the world, based on social interactions of minds in which people are concerned about each other's mental states.

The last two tests were used to examine the more advanced theory of mind reasoning ability in the cases. The strange stories test assesses the ability to infer mental states in a story context for social understanding. We selected seven stories for each case: pretence; lie; white lie; figure of speech; double bluff; irony; and persuasion. A previous study reported that subjects with autism-spectrum disorders show impaired provision of context-appropriate mental state explanations for strange stories, compared to normal control subjects (Happé, 1994).

As well as the strange stories test, we used the faux pas recognition test to assess the ability to recognize inappropriate statements in a story context (Baron-Cohen et al., 1999). We selected the original 10 faux pas stories and 10 control stories with no faux pas for TO and 7 faux pas stories and 7 control stories for HC, due to reported fatigue during testing. Subjects were presented with each story and asked whether a faux pas was contained. If a faux pas was detected, they were then asked for an explanation of it. We also requested that each subject answer two additional questions to test story comprehension in each story, to see whether a comprehensive understanding of each story was achieved. Baron-Cohen et al. (1999) reported that subjects with autism-spectrum disorders show impaired detection of faux pas on the faux pas recognition test compared to normal control subjects, despite intact story comprehension.

In addition, TO and HC were required to complete all 50 items in the Autism-Spectrum Quotient (AQ) questionnaire (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001). This questionnaire was developed as a self-administered method of screening for adults with normal intelligence and traits associated with autism-spectrum disorders. Score ranges from 0 to 50 in the questionnaire. Adults with Asperger syndrome or high-functioning autism show a mean score of 35.8, significantly higher than controls with a mean score of 16.4 (Baron-Cohen et al., 2001). Another recent study has shown that the threshold score for suspected Asperger syndrome or high-functioning autism is 26.0 (Woodbury-Smith, Robinson, Wheelwright, & Baron-Cohen, 2005). The present study used the Japanese version of the questionnaire, for which significantly high reliability has been shown in test–retest and inter-rater measures (Wakabayashi, Tojo, Baron-Cohen, & Wheelwright, 2004). In this version, adults with Asperger syndrome or high-functioning autism show a mean score of 37.9, significantly higher than controls with a mean score of 18.5 (Wakabayashi et al., 2004).

RESULTS

Theory of mind tests

Both cases passed the first- and second-order false belief tests, providing expected answers suggesting a proper understanding of each story. In terms of advanced theory of mind tests, both

cases showed good performance on the strange stories test. Overall percentage of providing appropriate explanations for given stories was 85.7% (just one error out of seven) in TO and 100% in HC on the strange stories test. On the faux pas recognition test, the percentage of detecting faux pas and having appropriate explanations was 60.0% in TO and 100% in HC for the provided faux pas stories. In contrast, the percentage of detecting "no" faux pas was 70.0% in TO and 57.1% in HC for the provided control stories. Both cases thus reported faux pas even in control stories without any faux pas. In addition, both cases showed higher scores on the two questions for story comprehension (92.5% for TO and 89.3% for HC).

Autism-spectrum quotient

AQ scores were 31 for TO and 29 for HC, above the threshold score for Asperger syndrome or high-functioning autism of 26 as defined by Woodbury-Smith et al. (2005). Interestingly, both cases spontaneously reported just after completing the questionnaire that they were sure that some of the personality traits focused on in the questionnaire identified the actual personality changes they felt. We then asked them to complete the AQ again for what they supposed their original personality was before surgery. AQ scores for purported pre-surgical state of the two cases were 13 for TO and 23 for HC, much lower than the initial scores and below the threshold score for Asperger syndrome or high-functioning autism. Both cases thus appear to have developed some autistic personality traits following surgical operations. All items representing autistic personality traits developed after surgical operations in both cases are listed in Table 2.

A general finding was that the two cases had developed some characteristics of autism after surgical operations. To specify these characteristics in greater detail, we compared those items to items identified in a two-factor structure model (Hoekstra, Bartels, Cath, & Boomsma, 2008). Two factors were identified among all 50 items in the AQ, namely "social interaction" factor and "attention to detail" factor. In TO, all 18 items fell into the "social interaction" factor, while in HC, 6 of 7 items fell into the "social interaction" factor (Table 2). The only item falling into the "attention to detail" factor in HC was item 9, which showed that he had become fascinated by dates.

TABLE 2
All items representing development of autistic personality traits after surgical operations in both cases

TO
Items changing from *definitely disagree* or *slightly disagree* to *definitely agree* or *slightly agree*
(4) I frequently get so strongly absorbed in one thing that I lose sight of other things.
(13) I would rather go to library than a party.
(16) I tend to have very strong interests, which I get upset about if I can't pursue.
(20) When I'm reading a story, I find it difficult to work out the characters' intentions.
(21) I don't particularly enjoy reading fiction.
(22) I find it hard to make new friends.
(35) I am often the last to understand the point of a joke.
(45) I find it difficult to work out people's intentions.
(46) New situations make me anxious.
Items changing from *definitely agree* or *slightly agree* to *definitely disagree* or *slightly disagree*
(8) When I'm reading a story, I can easily imagine what the characters might look like.
(10) In a social group, I can easily keep track of several different people's conversations.
(14) I find making up stories easy.
(17) I enjoy social chit-chat.
(25) It does not upset me if my daily routine is disturbed.
(38) I am good at social chit-chat.
(44) I enjoy social occasions.
(47) I enjoy meeting new people.
(48) I am a good diplomat.

HC
Items changing from *definitely disagree* or *slightly disagree* to *definitely agree* or *slightly agree*
(9) I am fascinated by dates.
(42) I find it difficult to imagine what it would be like to be someone else.
(45) I find it difficult to work out people's intentions.
Items changing from *definitely agree* or *slightly agree* to *definitely disagree* or *slightly disagree*
(8) When I'm reading a story, I can easily imagine what the characters might look like.
(10) In a social group, I can easily keep track of several different people's conversations.
(11) I find social situations easy.
(25) It does not upset me if my daily routine is disturbed.

Notes: The number in the top of each item indicates the item number in the AQ questionnaire (Baron-Cohen et al., 2001).

In another opportunity separate from the present study, we asked 11 cases with damage to other parts of the brain (orbitofrontal lesion, $n = 3$; basal forebrain lesion, $n = 3$; dorsolateral prefrontal lesion, $n = 2$; medial temporal lesion, $n = 1$; amygdala lesion, $n = 1$; and traumatic brain injury, $n = 1$) to complete the AQ, to compare

scores and possible personality changes detected by the AQ. Mean score for the 11 cases was 17. 0 (range 9–25), and median score was 17.0. All cases declared that personality traits identified on the AQ were unchanged after surgical operations or closed-head injuries.

DISCUSSION

In this study, we presented two cases with damage to the medial PFC and reported performance on various theory of mind tests, personality changes, and behavioral disturbances in daily activities. The two cases displayed damage basically limited to the medial PFC and showed mild difficulties in memory performance in daily activities, but no serious problems in language activities and executive functions. These patterns of results are basically consistent with previous case studies regarding damage to the same area of the brain (Baird et al., 2006; Bird et al., 2004). Concerning theory of mind tests, performance in the first- and second-order false belief test was perfect in both cases. Performance in the advanced theory of mind tests in TO was slightly impaired regarding the provision of appropriate explanations in the strange stories test and was considerably impaired in the identification of inappropriate verbal expressions for given contexts in the faux pas detection test. In contrast, performance in advanced theory of mind tests in HC was not impaired at all in either test. An interesting finding in both cases was that a faux pas was often reported even in control stories without any obvious faux pas.

The notable finding was that both cases showed some difficulties on the faux pas recognition test. The percentage of detecting faux pas and providing appropriate explanations in HC was 100%, compared to 60.0% in TO. Lower performance by TO may have been caused by deficits in delayed recall performance as found in WMS-R and ROCFT (Table 1). Although TO showed higher scores on the two questions for story comprehension (92.5%), he experienced difficulty in recalling the exact story contents. In fact, TO reported the presence of faux pas for all 10 faux pas stories, but could not recall what the exact contents were in each story. Taking these facts into account, his basic performance for detecting faux pas may not have been greatly reduced.

In contrast, both subjects sometimes incorrectly reported faux pas even in stories containing no faux pas, although they could correctly recognize faux pas in stories containing faux pas. Various factors could explain this pattern of results. First, this pattern could result from perseveration of response in both cases. The response for detecting faux pas could be a prevailing response, as half of the questions in the faux pas test did contain faux pas. However, no strong evidence of perseveration was found in either case, since we found very few total perseveration errors on WCST. Second, the pattern could result from general difficulty in understanding global contexts in complex situations. If this were the case, the subjects would show some problems in detecting faux pas in stories containing faux pas. However, the results were in direct opposition to this prediction. A final possibility is overcompensation. In a psychiatric sense, this is often defined as an attempt to overcome an actual defect or unwanted trait by exaggerating in the opposite direction. Self-reports from the two cases indicated that personality change extended to abnormal feelings in some emotional dimensions. Unfortunately, we did not perform any questionnaires examining anxiety traits, even though both subjects reported anxiety after surgery. These changes may have resulted in subjects being more sensitive to verbal expressions compared to before surgery. The explanation of overcompensation is considered the most plausible for understanding the over-detection of faux pas.

The most interesting finding in the present study was that the two cases showed personality changes after surgery, resulting in some characteristics of autism. These tendencies were mainly clarified by findings from the AQ questionnaire. According to the self-reports shown in Table 2, both cases showed a lack of theory of mind ability in everyday life, reduced spontaneous seeking to communicate with others after surgery, and obsessive focus on a single subject. To elucidate greater detail of those characteristics, we compared those items to the items identified in a two-factor structure model (Hoekstra et al., 2008). As a result, 25 items among the total 26 items for the development of autistic personality traits after surgical operations in both cases fell into the "social interaction" factor. This basically identified acquired functional deficits following damage to the medial PFC as a lack of social interaction. Surprisingly, HC even reported

becoming fascinated by dates, which is considered a strong characteristic of autism. Our results for the number of cases with damage to other areas besides the medial PFC revealed that these personality changes resulted from damage to the medial PFC alone.

However, there are limitations to the interpretation of the present results. We asked the cases to fill out the same questionnaire (AQ) twice, and requested on the second trial that they answer from the perspective of their previous personality before surgery. This obviously represents a "retrospective report" in the post-operative period, and the data are clearly of questionable validity. However, the second AQ trial based on self-reports revealed that some personality traits identified by the questionnaire matched well with actual personality changes reported after surgery. This suggests that results of the second trials were substantially valid. The results were consistent with previous imaging studies for Asperger syndrome, showing that the medial PFC is highly involved in understanding theory of mind stories compared to understanding control stories in normal control and Asperger syndrome groups, although level of peak activation was lower in the Asperger group (Happé et al., 1996). Another interpretation of the AQ rise in both cases is the effect of increased depression and/or anxiety. TO and HC both mentioned feeling depressive and anxious in everyday life. Depression and/or anxiety alone might increase the AQ score. However, most of our control cases with damage to other areas beside the medial PFC reported feeling more or less depressed and anxious, but did not show any increase in AQ score after the damage. This evidence suggests that depression or anxiety alone may not greatly affect AQ score.

In terms of laterality of damage in the medial PFC, clarifying differences in the extent to which cases show damage in each hemisphere is generally difficult (Gilbert, Williamson, Dumontheil, Simons, Frith, & Burgess, 2007). As mentioned above, some previous results support the notion that right hemisphere damage shows as impaired understanding of materials requiring attribution of mental state (Happé et al., 1999). More precise examinations of the present results in the two cases suggest that left-sided damage (TO) resulted in greater acquisition of autism traits than right-sided damage (HC). In contrast, oversensitivity in faux pas tests was relatively more associated with right-sided damage (HC) than left-sided damage (TO). Whether these dissociative patterns of results with laterality in the medial PFC are essential remains unclear. This inference is consistent with a previous study that reviewed the effect of laterality on theory of mind deficits and found no clear distinction in terms of the laterality of damage (Bird et al., 2004). Further studies are required to clarify this issue.

We were also able to determine the exact location of damage in the medial PFC. Amodio & Frith (2006) reported that the more posterior region of the rostral medial PFC is activated by cognitive tasks (e.g., action monitoring and attention), whereas the more anterior region of the rostral medial PFC is activated by emotional tasks (e.g., rating emotional responses to pictures of varying valence) according to a meta-analysis of task-related neural activations observed in the medial PFC. From these perspectives, TO displayed major damage in the more posterior region of the medial PFC, whereas HC showed major damage to the more anterior region of the medial PFC. Although TO's scores on neuropsychological tests showed no declines in executive functions, scores for attention and concentration and for delayed memory in WMS-R were mildly declined. This suggests that TO experienced some minor deficits in attention functions, consistent with the notion expressed by Amodio & Frith (2006), and also suggests that his amnesic syndrome resulted in lower scores in advanced theory of mind tests. Moreover, the result that TO showed greater acquisition of autism traits than HC seems to be explained by greater declines in social interaction, caused by reduced higher cognitive functions and the following reduced motivation to social communications. This explanation is consistent with some previous studies suggesting that dorsal areas within the PFC are highly involved in social behavior, along with the orbitofrontal cortex (Hornak et al., 2003; Mah, Miriam, & Grafman, 2004; Rudebeck, Bannerman, & Rushworth, 2008).

However, performance in theory of mind tests was less impaired for HC, who displayed major damage to the more anterior region of the medial PFC, than for TO. This is consistent with the previous study (Bird et al., 2004) and is inconsistent with the concepts of Amodio and Frith (2006). The anterior medial PFC is presumably required for efficient realization in theory of mind reasoning, but such reasoning may receive support from other brain areas besides the medial PFC in adults. If the anterior medial PFC plays an important role in theory of mind reasoning