prolongation of the ventilatory cycle,[34] possibly resulting in the prolongation of apnoeic events, especially in patients with heart failure.[35,36]

In conclusion, the present results show that episodes of apnoea are prolonged during periods of NREM sleep in the progression of the nocturnal sleep course, especially in the supine position in patients with severe OSA. It is hoped that this study will encourage further studies designed to examine changes in blood pressure during the course of sleep, especially taking into consideration the aggravation of OSA in the latter part of the night, and thereby confirming the relationship between OSA and the time-dependent increase in the risk of cardiovascular events.

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Epileptic, organic and genetic vulnerabilities for timing of the development of interictal psychosis

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Background
Age at the first psychotic episode and an interval between the onset of epilepsy and that of psychosis reflect developmental processes of interictal psychosis. However, factors relating to these indices remain unknown.

Aims
To identify clinical variables that are associated with the timing of the development of interictal psychosis.

Method
In 285 adults with epilepsy with interictal psychosis, effects of epileptic (epilepsy type), organic (intellectual functioning) and genetic (family history of psychosis) variables on timing of the development of psychosis were examined.

Results
The mean interval between the onset of epilepsy and that of psychosis was 14.4 years. Some psychosis occurred within a few years of the first seizure. Generalised epilepsy, normal intellectual function and a positive family history of psychosis were associated with early onset of psychosis.

Conclusions
Early development of interictal psychosis in people with epilepsy may reflect other individual vulnerabilities to psychosis rather than epilepsy-related damage.

Declaration of interest
None.

Interictal psychosis in epilepsy was first studied systematically by Slater and his colleagues.[1] They reported three main pieces of evidence to delineate interictal psychosis (called schizophrenia-like psychosis in the paper) as a distinct entity from schizophrenia: psychopathological characteristics, psychosis occurring after the development of epilepsy and no genetic loading for schizophrenia. Subsequent studies have formed a general consensus that interictal psychosis is mainly related to various epilepsy-related factors such as type of epilepsy, seizure types and laterality and locality of electroencephalogram (EEG) abnormalities, rather than non-specific demographic factors.[2] However, studies on interictal psychosis have shown contradictive findings that some of the demographic characteristics such as intellectual function[3,4] and family history of psychosis[5] were associated with occurrence of interictal psychosis. This is similar to the positive associations between these demographic factors and a high risk of functional psychoses such as schizophrenia. Using a comprehensive, multicentre database of patients suffering from epilepsy with and without psychosis, our group has found that interictal psychosis occurred more frequently in individuals with certain risk factors, including partial epilepsies, complex partial seizures, generalised tonic–clonic seizures, earlier onset of epilepsy and borderline intellectual function.[6] Most of these risk factors were also common in different types of epilepsy psychoses (e.g. interictal, postictal and bimodal psychoses),[7] but some factors historically known as risk factors for interictal psychosis were not extracted with multivariate analyses because they overlapped or interacted with others.[6–8]

Age at the time of the first psychotic episode and the time interval between the onset of epilepsy and that of psychosis are key elements of studies in interictal psychosis, as these age-related variables likely reflect neurodevelopmental and/or neurodegenerative processes in the brain.[9] Indeed, Slater *et al*[1] showed that patients with interictal psychosis tend to suffer their first seizure in early adolescence, with psychosis developing in their late twenties or thirties (approximately 15 years after the onset of epilepsy). They interpret the long interval, during which epilepsy and its consequences could cause further damage to the brain, as a preparatory period for generation of psychosis. Whereas many studies have reported similar age-related variables,[2] some have suggested the interval is an artefact as a result of the wide range of distribution of time intervals and to the tendency of a shorter interval in individuals with late-onset epilepsy.[10,11] In our previous study,[12] age at onset of psychosis in a subgroup of patients with chronic interictal psychosis was comparable with that in those with schizophrenia, whereas the age at onset was more advanced in the whole group of patients with interictal psychosis (both episodic and chronic). We also showed no difference between various types of partial epilepsies in age at onset of psychosis and in time intervals.[8] However, few studies have examined the contributions of the other clinical factors to age-related variables; thus, it remains unknown whether particular clinical factors are related to the timing of development of interictal psychosis. In the current study, we investigated the timing of development of interictal psychosis in association with epilepsy-related and demographic characteristics in a large cohort of patients with interictal psychosis.

Method

Definition of interictal psychosis

In our study, psychosis was defined as the presence of hallucinations, delusions or a limited number of severe abnormalities of behaviour in accordance with the ICD–10.[13] The operational criteria for interictal psychosis were as follows: the psychosis developed after the onset of epilepsy;[1,14,15] the psychotic episodes occurred with no distinct antecedent seizures when the patient was seizure-free or between habitual seizures;[6,7] psychotic episodes lasted 24 h or more in a state of full consciousness. Interictal

psychosis included chronic schizophrenia-like psychosis (at least one episode lasting 1 month or more) and brief (acute, episodic) interictal psychosis (all episodes resolved within 1 month).[1,16–18] Postictal psychosis, which occurred within 7 days after a decisive seizure or cluster of seizures,[7,17,19] and ictal psychotic phenomenon[17] were excluded.

Participants

All participants met the criteria for epilepsy as set forth in the 1989 International Classification of Epilepsies and Epileptic Syndromes.[20] The participants all attended one of five institutions with adult epilepsy clinics: National Centre Hospital for Mental, Nervous, and Muscular Disorders; Nihon University Hospital; Tokyo Medical University Hospital; Tokyo Medical and Dental University Hospital; or Komagino Hospital. The five epilepsy clinics cover the greater Tokyo area of a population of approximately 35 million as the main neuropsychiatric institutions for adults with epilepsy. In addition, the National Centre Hospital is the only institution in the country that has a neuropsychiatric in-patient unit dedicated to patients with epilepsy, accepting tertiary referrals from outside the catchment area. Since August 1996, these epilepsy clinics have maintained a collaborative database designed specifically for epilepsy psychosis.[6–8,12] Our previous studies[6–8,12] were based on the database with patients who had been registered until the end of 1996. The current study was conducted with a data-set entered until December 2000, with a total of 313 patients with epilepsy and interictal psychotic episodes being identified. To focus on interictal psychosis, 19 patients with bimodal psychosis, who exhibited both interictal and postictal psychoses in distinct periods,[7] were excluded from the study. Five patients with epilepsy resulting from a neurodegenerative disorder and four without sufficient clinical information regarding the epilepsy were also excluded. Consequently, 285 patients with interictal psychosis were enrolled in the study. No participants showed evidence of substance misuse, dementing process or a recent progressive space-occupying lesion.

Variables studied

We investigated the following variables:

(a) age at the time of investigation;

(b) gender;

(c) family history of psychosis, i.e. any psychotic disorder (schizophrenia, other paranoid disorder, acute transient psychosis, etc.) in a first-degree relative, according to the Japanese version of the Family History Research Diagnostic Criteria;[21]

(d) age at the onset of epilepsy, i.e. age at the time of the first afebrile seizure;

(e) type of epilepsy based on ictal symptoms, EEG findings and neuroimaging in accordance with the International Classification of Epilepsies and Epileptic Syndromes[20] (i.e. localisation-related epilepsies and generalised epilepsies, including idiopathic and symptomatic);

(f) intellectual functioning: impaired (full-scale IQ on the Wechsler Adult Intelligence Scale–Revised[22] of 70 or below), borderline (of 71–84), or normal (of 85 or above) in accordance with the DSM–IV;[23]

(g) age at onset of psychosis (i.e. age at the time of the first psychotic episode);

(h) time interval between the onset of epilepsy and that of psychosis, calculated as age at onset of psychosis minus age at onset of epilepsy.

As different neuroimaging techniques were used during different time periods and by each institution, neuroimages were used only for diagnostic information. Diagnoses and evaluations were made by consultant neuropsychiatrists qualified in both psychiatry and epileptology. The study was approved by the ethics committees of the institutions.

Data analysis

Differences in linear variables (ages) for the categorical variables (gender, epilepsy type and family history) were subjected to analysis of variance (ANOVA). Correlation between categorical variables was examined by means of the chi-squared test or Fisher's exact test. Correlations between linear or rank-order variables (intellectual functioning) were examined by means of simple regression analysis or Spearman's rank-order correlation coefficient. Because age at the time of examination was correlated significantly with the other age-related variables (age at the onset of epilepsy ($r=0.39$, $P<0.0005$), time interval ($r=0.31$, $P<0.0005$), and age at the onset of psychosis ($r=0.62$, $P<0.0005$)), the weighted least squares procedure (weighted by age at the time of examination) was applied.[12] A P-value of <0.05 was considered significant. All statistical analyses were performed with the Statistical Package for Social Sciences (SPSS) 14.0 for Windows.

Results

Clinical characteristics of the 285 patients with interictal psychosis were as follows: mean age at the time of examination was 40.7 years (s.d. = 12.8, range 19–76, median 39). There were 146 men and 139 women. A total of 236 patients had localisation-related epilepsies and 49 generalised epilepsies (34 with idiopathic and 15 with symptomatic generalised epilepsies). With respect to estimated aetiologies of epilepsy, there were 22 patients with central nervous system infections, 26 with birth complications (including cerebral palsy), 15 with head trauma, 7 with brain tumours, 16 with migration disorders or other malformation, 5 with vascular disorders, and pathogenesis was unknown for the remaining 194 patients. Intellectual function was normal in 140 patients, borderline in 55, and impaired in 90. There were 244 patients with chronic schizophrenia-like psychosis, 27 with brief interictal psychosis and 14 with interictal psychosis of unknown duration. Twenty-one patients had a family history of psychosis.

Distributional relations between the patients' characteristics studied were as follows: gender and intellectual functioning ($\chi^2=2.6$, $P=0.280$), gender and epilepsy type (129 men and 107 women with localisation-related epilepsies, 17 men and 32 women with generalised epilepsies; $\chi^2=5.7$, $P=0.017$), gender and family history of psychosis ($\chi^2=0.11$, $P=0.736$), intellectual functioning and epilepsy type ($\chi^2=4.1$, $P=0.126$), intellectual functioning and family history of psychosis ($\chi^2=0.44$, $P=0.802$), and epilepsy type and family history of psychosis ($\chi^2=0.06$, $P=0.767$).

Age-related factors observed were as follows: mean age at onset of epilepsy was 11.7 years (s.d = 8.0, range 0–51, median 11), mean age at onset of psychosis was 26.1 years (s.d. = 9.6, range 12–65, median 24) and the mean time interval between the onset of epilepsy and that of psychosis was 14.4 years (s.d. = 9.3, range 0–51, median 13). Distribution of the time intervals for the entire patient group are shown in Fig. 1. Age at onset of psychosis correlated significantly with that of epilepsy ($r=0.47$, $P<0.0005$) and with the time interval ($r=0.64$, $P<0.0005$).

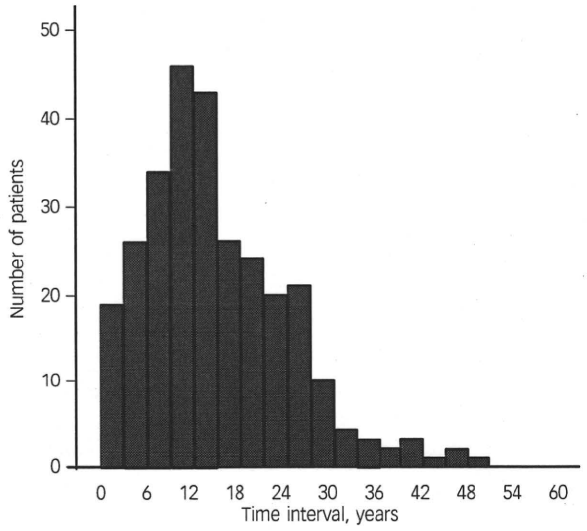

Fig. 1 Distribution of the time intervals (years) between the onset of epilepsy and that of interictal psychosis (mean 14.4 years, s.d. = 9.2, range 0–51, median 13).

The time interval was 3 years or less in 31 patients (10.9%), 5 years or less in 45 (15.8%), 10 years or less in 101 (38.6%).

The time interval also correlated significantly with age at onset of epilepsy ($r = -0.38$, $P < 0.0005$).

The estimated marginal means of age at onset of epilepsy, age at onset of psychosis and the time interval for each variable are shown in Table 1. The time interval and age at onset of psychosis differed significantly between epilepsy types: interictal psychosis developed at an earlier age and with a shorter interval in patients with generalised epilepsies, in particular with idiopathic generalised epilepsies, than those in patients with localisation-related epilepsies. Intellectual functioning correlated significantly with age at onset of epilepsy and the time interval: the onset of epilepsy was earlier and the interval was longer in those patients with intellectual disturbances than in those without. The onset of psychosis was significantly earlier in patients with a family history of psychosis than in those without.

We carried out further analyses on the participants with localisation-related epilepsies ($n = 236$) and obtained similar tendencies: intellectual functioning correlated significantly with age at onset of epilepsy ($r = 0.293$, $P < 0.0005$; impaired, estimated marginal mean 9.3 (s.e. = 1.1), borderline 11.3 (s.e. = 1.2), normal 15.3 (s.e. = 0.8)), with age at onset of psychosis ($r = 0.128$, $P = 0.049$; impaired 26.3 (s.e. = 1.4), borderline 29.8 (s.e. = 1.6), normal 30.0 (s.e. = 1.0)) or with time interval ($r = -0.157$, $P = 0.016$; impaired 17.0 (s.e. = 1.2), borderline 18.5 (s.e. = 1.4), normal 14.6 (s.e. = 0.9)). Likewise, in the family history of psychosis of the participants with localisation-related epilepsies, the estimated marginal mean age at onset of psychosis also differed significantly ($F = 5.45$, $P = 0.020$; positive 22.7 (s.e. = 2.8), negative 29.4 (s.e. = 0.8)). However, there was no significant difference in age at onset of epilepsy ($F = 1.33$, $P = 0.250$; positive 10.3 (s.e. = 2.3), negative 13.0 (s.e. = 0.6)) or in time interval ($F = 2.33$, $P = 0.129$; positive 12.4 (s.e. = 2.5), negative 16.4 (s.e. = 0.7)).

Discussion

In the current study, age at onset of interictal psychosis and time interval between onset of epilepsy and that of psychosis varied

Table 1 Estimated marginal mean (standard error, 95% CI) years for age-related variables per clinical variables (total $n = 285$)

		Age at onset of epilepsy				Age at onset of psychosis				Time interval			
	n	Mean (s.e.)	95% CI	Test statistic	*P*	Mean (s.e.)	95% CI	Test statistic	*P*	Mean (s.e.)	95% CI	Test statistic	*P*
Gender[a]				$F = 0.15$	0.696			$F = 0.00$	0.984			$F = 0.09$	0.765
Men	146	12.5 (0.7)	11.1–13.9			27.9 (0.9)	26.2–29.7			15.4 (0.8)	13.8–17.1		
Women	139	12.9 (0.7)	11.4–14.3			28.0 (0.9)	26.2–29.8			15.1 (0.8)	13.4–16.7		
Intellectual functioning[b]				$r = 0.305$	<0.0005			$r = 0.106$	0.074			$r = -0.167$	0.005
Impaired	90	9.6 (0.9)	7.8–11.4			25.6 (1.2)	23.3–27.9			16.1 (1.1)	14.0–18.3		
Borderline	55	11.4 (1.1)	9.2–13.6			29.1 (1.4)	26.3–32.0			17.8 (1.3)	15.2–20.4		
Normal	140	15.0 (0.7)	13.6–16.4			28.8 (0.9)	27.1–30.6			13.8 (0.8)	12.2–15.4		
Epilepsy type[a]				$F = 0.25$	0.615			$F = 13.2$	<0.0005			$F = 12.0$	0.001
Localisation-related epilepsies	236	12.8 (0.6)	11.7–13.9			29.1 (0.7)	27.8–30.5			16.2 (0.6)	15.0–17.5		
Generalised epilepsies	49	12.1 (1.3)	9.5–14.7			22.8 (1.6)	19.6–26.0			10.6 (1.5)	7.7–13.6		
Idiopathic	34	12.7 (1.0)	10.6–14.8			22.5 (1.0)	20.5–24.6			9.8 (1.3)	7.1–12.5		
Symptomatic	15	10.7 (1.5)	7.6–13.8			23.0 (1.5)	20.0–26.0			12.3 (1.9)	8.4–16.2		
Family history of psychosis[a]				$F = 1.23$	0.268			$F = 5.33$	0.022			$F = 2.28$	0.132
Positive	21	10.6 (1.9)	6.8–14.4			22.6 (2.4)	17.9–27.3			12.0 (2.2)	7.6–16.4		
Negative	264	12.8 (0.5)	11.8–13.9			28.4 (0.7)	27.1–29.7			15.5 (0.6)	14.3–16.7		

a. By analysis of variance with weighted least squares procedure (weighted for age at the examination).
b. By Spearman rank-order correlation coefficient.

considerably. Participants with generalised epilepsy, normal intellectual function or a positive family history of psychosis tended to show an early onset of interictal psychosis.

Distribution of the time interval

The mean interval between the onset of epilepsy and that of psychosis was 14.4 years, consistent with previously reported data.[1,2] This interval varied widely among patients, not showing a simple bell-curve distribution. The wide variation may be in part accounted for by the cumulative effects of various epilepsy-related factors on the development of interictal psychosis, i.e. repeated seizures, frequent epileptic discharges in the brain, adverse effects of anti-epileptic drugs and psychosocial stress.[2,18] However, it is important to note that interictal psychosis developed in a considerable number of patients shortly after their first epileptic event (within a few years). Indeed, this fact has been described in previous studies.[1,11] It is not likely that such quick development of interictal psychosis is as a result of the epilepsy-related process alone. There is little evidence that occurrence of interictal psychotic symptoms is precipitated by a higher impact of particular epilepsy processes (e.g. excessive seizures and extensive epileptogenesis),[17] although severe epilepsy can be a risk factor for the development of psychosis. Thus, in addition to the epilepsy-related process, the presence of certain preparatory conditions, such as individual vulnerabilities to psychosis[24] that may be common to organic psychoses or even functional psychoses, may play a role in generating psychotic symptoms in individuals with epilepsy.

Epilepsy type

The interval between onset of epilepsy and that of psychosis was significantly shorter in patients with generalised epilepsies than in those with localisation-related epilepsies, with the onset of epilepsy being comparable among these two groups. Patients with generalised epilepsies, unlike those with localisation-related epilepsies, tend to have fewer epilepsy (organic)-related risk factors for psychosis, i.e. no distinct brain insult, low seizure frequency, simple medications and normal cognitive functioning, which may be associated with a reduced frequency of development of interictal psychosis.[2,6] It is possible that patients with generalised epilepsies in whom interictal psychosis develops might be affected by non-epileptic precipitators of psychosis. This may be similar to the difference between patients with schizophrenia and those with epilepsy; psychosis is observed at a more advanced age in patients with epilepsy than in patients with schizophrenia that does not involve distinct brain damage.[12] Among patients with generalised epilepsies, only those with a strong vulnerability may suffer interictal psychosis at an early age regardless of acquired brain insults because of epilepsy.

Intellectual functioning

Our patients with normal intellectual functioning exhibited interictal psychosis sooner after the onset of epilepsy. This finding was also seen in the subgroup of participants with localisation-related epilepsies only. Impaired intellectual function is often associated with severe epilepsy and brain damage,[25] although it is also observed in people without such conditions.[26] Functional psychosis develops two to three times more frequently in people with impaired intellectual functioning than is reported in the general population.[26,27] Moreover, psychosis develops 1.3–4.7 times more frequently in patients with epilepsy with impaired intellectual functioning than in those without.[7] In contrast, normal intellectual functioning usually suggests having less brain damage and is not related to increased risks for the development of psychosis. Why do patients with a lower risk suffer psychosis earlier than those at a higher risk? Again, psychosis may develop more quickly in patients with normal intellectual functioning who have strong congenital vulnerabilities to psychosis than in those with acquired organic precipitators, i.e. intellectual dysfunction and epilepsy, but without such vulnerabilities.

Family history of psychosis

We have shown that interictal psychosis develops at an earlier age in patients with a family history of psychosis than in those without. A genetic tendency towards psychosis in patients with epilepsy has long been underestimated[2] since Slater's initial study.[1] However, large studies have shown that genetic factors play a significant role in the development of psychosis in patients with epilepsy.[5,6] These findings appear to be similar to those found in functional psychosis (i.e. schizophrenia); people with a positive family history tend to have a higher risk of psychosis and to exhibit their first psychotic symptoms earlier than those without.[28,29] A positive family history of psychosis may be a universal risk factor for developing psychosis, and it appears to reflect, at least in part, a congenital vulnerability to psychosis.[23] Even in patients with epilepsy and a positive family history of psychosis, psychotic symptoms are likely generated sooner regardless of acquired risk factors related to either epilepsy or brain damage.

Study limitations

Some limitations should be considered in relation to the current study. Analysis of age at onset of psychosis in patients with epilepsy is subject to some methodological issues.[10] Because epilepsy psychosis was defined operationally as psychosis developing after the onset of epilepsy in accordance with Slater & Roth's definition,[14] two patient groups were excluded: patients in whom psychosis developed before epilepsy[17] and patients in whom novel psychoses will develop after the time of the investigation or who died before the possible development of psychosis. However, neither group would have been large enough to markedly influence mean age at onset of psychosis or the mean time interval between onsets of the two disorders. Neither of these omissions explains the significant differences in age at onset of psychosis or in the onset interval between patients with particular clinical characteristics. In addition, despite the large cohort of participants with interictal psychosis, the number of patients in whom particular factors were analysed, such as a positive family history of psychosis and generalised epilepsies, was insufficient to produce strong statistical power. Factors that we did not consider may be associated with age-related factors, but would not have affected the result of our study. Although our findings point to the effects of certain vulnerabilities to psychosis (reflected by a positive family history), it is still unclear what these vulnerabilities are. Evidence supporting such vulnerability concepts is scarce, even for patients with functional psychosis.[24]

Results of the current study show some relationship between age at onset of interictal psychosis and several clinical variables that may reflect individual vulnerabilities. These vulnerabilities, in addition to epilepsy-related deficits, can affect the generation of interictal psychosis independently or interactively. Further comprehensive studies to confirm such vulnerabilities are required.

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Regular Article

Functional magnetic resonance imaging study on the effects of acute single administration of paroxetine on motivation-related brain activity

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Aim: The aim of the present study was to investigate the effects of acute paroxetine administration on brain activity related to motivation.

Methods: Sixteen healthy subjects participated in a randomized, single-blind, no-drug/placebo-controlled, cross-over study. After administration of no drug, placebo or paroxetine (selective serotonin reuptake inhibitor; 20 mg), subjects underwent functional magnetic resonance imaging while performing a monetary incentive delay task. We analyzed the differences in brain activities of the reward anticipation/motor preparation period that are subject to motivational modulation. For this purpose, we subdivided the incentive trials on the basis of whether the reaction times (RT) were slower or faster than the subject's mean RT (slow RT and fast RT trials).

Results: No drug and placebo showed robust activation differences in the globus pallidus and putamen for the fast RT trials compared to the slow RT trials, whereas paroxetine showed none. Paroxetine showed significantly lower activations in the globus pallidus, insula, putamen and dorsolateral prefrontal cortex compared to no drug in the fast RT trials.

Conclusions: Paroxetine single acute administration diminished brain activity induced by motivation in healthy subjects. This may partially explain the increased lack of motivation seen in patients with relatively mild symptoms after taking a dose of paroxetine for the first time.

Key words: functional magnetic resonance imaging, motivation, paroxetine, reaction time, reward anticipation.

SELECTIVE SEROTONIN REUPTAKE inhibitors (SSRI) are first-line drugs for the treatment of major depressive disorder (MDD). MDD is characterized by disturbances in emotion, motivation and behavior in the presence of autonomic nervous symptoms.[1] A core symptom of MDD includes decreased motivation,[2,3] which SSRI sometimes rather aggravate in some patients.[4–6]

Motivational processing includes reward anticipation, motor preparation and related processes, including arousal and attention.[7,8] Several pharmacological functional magnetic resonance imaging (fMRI) studies have assessed the functions and/or mechanisms of SSRI related to motor, attention and reward. The effects of SSRI on motor function,[9,10] attention,[11] loss/no-loss comparison[12] and neural

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processing of both rewarding and aversive stimuli[13] in healthy subjects have been studied by fMRI. McCabe reported that seven days of citalopram treatment diminished the brain activity induced by deliveries of rewards and aversive stimuli. They used primary rewards, chocolate taste and unpleasant strawberry taste as stimuli. Their conclusion indicated that the results could explain the experience of emotional blunting described by some patients during SSRI treatment.[13–15]

Decrease in motivation is also clinically observed after taking an initial dosing.[16] We have clinically observed some patients, especially patients with mild symptoms who reported decreased motivation after taking an initial dose of SSRI. Then, in the present study, we focused on the effects of an SSRI single acute administration on brain activity during motor preparation and reward anticipation, which are subject to motivational modulation. For this purpose, we used a monetary incentive delay (MID) task.[17] This task has been used in numerous reward-processing studies, and variations of the MID task have been used in a variety of other research.[18–20] Regardless of the details, the reward anticipation/motor preparation period and the subsequent button press during the task are essential. It is likely that the subject's motivations fluctuate over repeated trials of the MID task, and this is reflected in reaction time (RT). We expected that paroxetine would attenuate brain activity induced by motivation.

METHODS

Subjects

Sixteen healthy subjects participated in this study, but two were excluded because of an extremely low hit rate (less than 60%). Fourteen healthy subjects (eight men, mean age ± SD: 31 ± 3.8 years) were included in the final analysis. All subjects were native Japanese speakers and right-handed, as assessed by the Edinburgh Handedness Inventory. They filled out a questionnaire about their medical history and medications and were then interviewed by a medical staff member. They had no history of present or past psychiatric illnesses, neurological disorders, significant physical illnesses or head injuries, and no alcohol- or drug-related problems. They had not taken any types of medication for at least 1 day prior to scanning.

After a complete explanation of the study, including the possible side-effects of paroxetine, written informed consent was obtained from all the subjects and all the subject identifiers were removed. The protocol was approved by the local ethics committee.

Drug administration

We chose paroxetine as the SSRI for this study because it has the highest affinity for the human serotonin (5-HT) transporter among SSRI and other antidepressants according to radioligand binding assay studies[21–23] with a reported equilibrium dissociation constant (K_D) of 0.13 ± 0.01 nmol.

All subjects were examined after administration of paroxetine (S, 20 mg [minimally effective dose] paroxetine hydrochloride hydrate tablet), placebo (P, 12 mg lactobacillus bifidus tablet) or no drug (N) in a randomized, single-blind, no drug/placebo controlled, cross-over design. Three to 43 days (average 14.0 ± 13.7 days) passed between experiments. The order of drug administration was counterbalanced across subjects. The drug administration order consisted of six combinations (N-P-S, N-S-P, P-N-S, P-S-N, S-N-P, S-P-N) and we randomly assigned each combination to each subject.

The maximum drug concentration time (Tmax) of paroxetine 20 mg was reported to be 5.05 ± 1.22 h in healthy Japanese subjects.[24] Accordingly, placebo (P) and paroxetine (S) were given 5–5.5 h before initiating scanning to ensure maximum and stable plasma concentrations.

A previous positron emission tomography study suggests that 80% 5-HT transporter blockade is important for therapeutic effect of SSRI.[25] A single dosing of minimum therapeutic dose of an SSRI showed around 80% 5-HT transporter occupancy, which was almost the same as long-term dosing data.[26] Accordingly, a single dosing of paroxetine 20 mg of this study should have enough 5-HT transporter occupancy for therapeutic effect.

Reward task

Subjects performed an incentive task during functional scanning after a short pre-scanning training task. The task paradigm was an event-related design. The task was created with E-Prime 1.2 (Psychology Software Tools), which consisted of 98 7–8-s trials with 4-s inter-trial intervals (approx. 19 min. total). During each trial, subjects were shown one of three cue shapes (500 ms), a fixed crosshair during a variable delay (2500–3500 ms), and they responded with

a button press during the presentation of a gray square target (500 ms). They were then shown a fixed yellow crosshair (3000 ms) and this was followed by feedback (500 ms) notifying subjects if they had gained the points indicated by the cue, gained no points (= 0 point), or failed to press the button within 500 ms. The inter-trial interval was set to 4000 ms.

The cues signaled the possibility of no gain, 0 points ($n = 10$; denoted by a circle), 100 points ($n = 44$; denoted by a circle with one horizontal line) or 500 points ($n = 44$; denoted by a circle with three horizontal lines). There were three pseudorandom and predetermined orders of trials presented to subjects depending on experimental order, i.e. the combinations of medication and trial presentation order were counterbalanced.

Before scanning, subjects were instructed that the duration of target presentation was fixed to 500 ms but the button press limits differed from trial to trial. Fourteen 100-point cue and 500-point cue trials were predetermined to have a feedback of 0 points despite any efforts. In eight of these 28 trials, RT were not collected and were excluded from the analysis. The other trials required a fixed 500-ms time limit for the button press. If the subject did not respond in the appropriate interval, the message 'Press the button!' was displayed. We asked subjects to respond as quickly as possible to gain the maximum number of points, but the points earned were not reflected in the payment for participation in the study. Subjects were also asked to respond within the target presentation time even if the cue was a circle without line (potential 0 points). The total points earned were displayed at the end of the session.

During the original MID task,[17] RT were collected during the practice session so that the task difficulty level was set to achieve a success rate of 66%. However, we fixed the target duration to 500 ms so that the hit rate would reflect subjects' efforts more accurately. We also performed more trials to compare the effects of differences of RT in incentive trials. To maintain cue incentives, predetermined trials of gain cued with non-gain feedback were intermixed. Subjects were not told of their running point totals to minimize possible confounding effects.

fMRI data acquisition

The fMRI scans were acquired with a 3T Siemens MAGNETOM Trio Tim system scanner (Siemens, Erlangen, Germany). A total of 575 functional images were taken with a T2*-weighted gradient echo planer imaging sequence (TE = 25 ms; TR = 2000 ms; FA = 90°; matrix 64 × 64; FOV 192 × 192 cm) sensitive to the blood oxygenation level dependent (BOLD) contrast. Whole brain coverage was obtained with 34 axial slices (thickness 4 mm; in-plane resolution 3 × 3 mm).

Behavioral data analysis

For each drug condition for each subject, the mean RT to the target was calculated. Trials in which subjects did not press the button within the time limit were excluded from this calculation. Since the goal of this study was to investigate motivational motor preparation, we divided the RT of the incentive trials (100 and 500 points) on the basis of whether the RT were slower or faster than the subject's mean RT (RTslow and RTfast). For the purpose of this analysis, the 100- and 500-point trials were pooled to increase the sample set; there were no significant differences in hit rate or proportion of successful button presses among drug conditions for the different point trials. The mean RT of the slow RT and the fast RT trials were calculated, and these data were entered into a 3 (drug: non-drug, placebo, and paroxetine) × 2 (RT: slow and fast)-repeated-measures ANOVA using SPSS 16.0 J (SPSS Japan, Tokyo, Japan). The level of significance was set at 0.05.

fMRI data analysis

Image pre-processing and data analysis were performed with the statistical parametric mapping software package, SPM5 (Wellcome Department of Imaging Neuroscience, London, UK) running MATLAB 2007a (Mathworks, Natick, MA, USA). During pre-processing, the echo planer images were corrected for sequential slice timing, and all images were realigned to the first image to adjust for possible head movements. The realigned images were then spatially normalized to a standard Montreal Neurological Institute (MNI) template.[27] After normalization, all scans had a resolution of $2 \times 2 \times 2$ mm^3. Functional images were spatially smoothed with a 3-D isotropic Gaussian kernel (full width at half maximum of 8 mm). Low-frequency noise was removed by applying a high-pass filter (cut-off period = 192 s) and the default correction for AR1 auto correlation was performed for the fMRI time series at each voxel. A temporal smoothing function

was applied to the fMRI time series to enhance the temporal signal-to-noise ratio. Significant hemodynamic changes for each condition were examined using the general linear model with boxcar functions convoluted with a hemodynamic response function. Statistical parametric maps for each contrast of t-statistic were calculated on a voxel-by-voxel basis.

We then assessed the RT effect for each drug condition and the drug effect for the slow or fast RT during reward anticipation. We divided the trials into slow and fast RT trials, and we created the t-contrasts for the anticipation period between the offset of cue presentation and the onset of target presentation for the three different drug conditions in single-subject analysis (Nslow, Nfast, Pslow, Pfast, Sslow, Sfast).

A random effects analysis was performed to examine for population-wide effects. First, we used a 3 (medication: no drug, placebo and paroxetine) × 2 (RT: fast and slow) full factorial design to investigate brain activation between the different RT trials under each drug condition. There were significant activations for Nfast > Nslow in basal ganglia and primary motor cortex of which evident correlations have been revealed with reward anticipation[17,18,28,29] and motor preparation,[30] whereas activations for Pfast > Pslow and Sfast > Sslow were almost none. Then, to focus on regional activations in the reward anticipation and motor preparation-related areas in placebo and paroxetine, after paired *t*-tests were applied to Nfast > Nslow at the $P < 0.001$ level, uncorrected, with a voxel threshold of k = 10, we proceeded to a region-of-interest (ROI) analysis.

RESULTS

Behavioral data

The average hit rate of 90 trials was 92.9 ± 5.5%, 95.5 ± 4.2%, and 92.8 ± 6.7% for no drug, placebo, and paroxetine, respectively.

The average RT of all the trials and of the incentive (100 and 500 points) trials were 297.42 ± 38.69 ms and 294.02 ± 42.66 ms, 294.03 ± 40.31 ms and 290.45 ± 46.69 ms, 299.77 ± 38.96 ms and 298.08 ± 44.72 ms, under no drug, placebo and paroxetine conditions, respectively. There were no significant differences among three drug conditions.

Then we subdivided the RT of each incentive trial based on their relationship to the subject's mean RT, and the mean RT of each group, RTslow and RTfast, were compared for each drug treatment group.

A 3 (drug: non-drug, placebo, and paroxetine) × 2 (RT: slow and fast)-repeated-measures ANOVA revealed an effect of RT, $F_{1,13} = 398.73$, $P < 0.001$. Post hoc analyses with Bonferroni correction showed significant differences between RTslow and RTfast for each drug condition. RTslow and RTfast were 329.70 ± 27.04 ms and 258.34 ± 19.12 ms, 327.64 ± 31.61 ms and 253.25 ± 24.36 ms, 334.74 ± 30.04 ms and 261.43 ± 20.26 ms under no drug, placebo and paroxetine conditions, respectively. However, no significant differences were detected in the same RT (slow or fast) group among the different drug conditions.

fMRI data

The significantly activated areas for Nfast > Nslow were left primary motor cortex (T = 8.50), left globus pallidus (GP) (T = 5.95), right GP (T = 5.14), left dorsolateral prefrontal cortex (DLPFC) (T = 5.57), left transverse temporal gyrus (T = 5.26), right transverse temporal gyrus (T = 5.26), left thalamus (T = 4.87), right thalamus (T = 3.53), left insula (T = 4.71), right insula (T = 4.69), left putamen (T = 4.41), right putamen (T = 4.57), vermis (T = 4.50), right nucleus accumbens (NAcc) (T = 4.49) and left caudate (T = 4.27).

To investigate motivation-related areas under placebo and paroxetine conditions, we then performed a ROI analysis for the peak voxel of the regions significantly activated in Nfast > Nslow whole brain *t*-test. The ROI were selected based on previous fMRI studies of reward anticipation; GP,[28] insula,[27,29] putamen,[17,18,29] NAcc,[17] caudate,[29] DLPFC[31] and motor preparation; primary motor cortex.[30] The MNI coordinates [x y z] of ROI were left GP [−24 −10 0], right GP [20 −10 0], left insula [−38 −14 10], right insula [40 2 8], left putamen [−22 8 −2], right putamen [28 4 8], right NAcc [10 10 −14], left caudate [−6 12 4], left DLPFC [−36 32 26] and left primary motor cortex [−32 −22 54]. We collected beta values of each ROI and entered the data into 3 (drug conditions: N, P, S) × 2 (RT: slow, fast)-repeated-measures ANOVA using SPSS 16.0J. The level of significance was set at 0.05.

This ROI analysis using an ANOVA with repeated measures revealed a significant interaction between drug and RT in left insula ($F_{2,26} = 4.406$, $P = 0.022$), right insula ($F_{2,26} = 5.379$, $P = 0.011$), right NAcc ($F_{2,26} = 3.387$, $P = 0.049$), left primary motor cortex ($F_{2,26} = 4.016$, $P = 0.030$), a significant drug effect in

right insula ($F_{1,13} = 6.948$, $P = 0.021$) and left primary motor cortex ($F_{2,26} = 7.894$, $P = 0.002$), a significant RT effect in left GP ($F_{1,13} = 1.573$, $P < 0.0001$), right GP ($F_{1,13} = 37.957$, $P < 0.0001$), right insula ($F_{1,13} = 6.948$, $P = 0.021$), left putamen ($F_{1,13} = 45.757$, $P < 0.0001$), right putamen ($F_{1,13} = 13.968$, $P = 0.002$), right NAcc ($F_{1,13} = 5.755$ $P = 0.032$), left caudate ($F_{1,13} = 10.553$, $P = 0.006$), left DLPFC ($F_{1,13} = 10.568$, $P = 0.006$) and left primary motor cortex ($F_{1,13} = 38.179$, $P < 0.0001$).

Post hoc analysis with Bonferroni correction showed there were significant differences between paroxetine and placebo in only the left primary motor cortex, Pslow and Sslow ($P = 0.003$), Pfast and Sfast ($P = 0.008$), in which the activations were greater under placebo treatment (Fig. 1j). In the absence of drug or placebo treatment, the fast RT trials (Nfast) showed significantly higher activation than the fast RT trials of paroxetine condition (Sfast) in left GP ($P = 0.023$), left insula ($P = 0.008$), right insula ($P = 0.007$), right putamen ($P = 0.008$), left DLPFC ($P = 0.022$) and left primary motor cortex ($P = 0.003$) (Fig. 1a,c,d,f,i,j), which was not shown in comparison between the slow RT trials. There were no significant differences between placebo and no drug in any of the ROI.

Considering the way the ROI were defined, it was natural that there were significant differences between Nslow and Nfast in all the ROI. In paroxetine conditions, Sfast was significantly more activated than Sslow in only the left primary motor cortex (Fig. 1j). When subjects were given placebo, Pfast activation was greater than Pslow only in the left GP ($P = 0.045$), left putamen ($P = 0.007$) and left primary motor cortex ($P = 0.042$) (Fig. 1a,e,j).

DISCUSSION

Disturbances in motivation and motor activity are seen in MDD and these symptoms are sometimes exacerbated by SSRI in some patients. To investigate this paradoxical effect, we wish to use fMRI to monitor affected patients in response to drug therapy. However, as a first step, we studied normal subjects following a single dose of the SSRI paroxetine.

In this collection of normal subjects, there were no differences among the three drug conditions within each of the average RT of the whole, no incentive, incentive and subdivided RT trials. Thus, paroxetine administration did not affect subject behavior or performance globally. The average RT of no incentive and incentive trials showed no significance, which might be induced by the instruction for the subjects to press the button within the short duration of 500 ms even when the cue was no incentive.

Then, we investigated brain activations between the slow RT and the fast RT trials, which were behaviorally subdivided with significance, within treatment groups. The fast RT trials recruited greater activation in the GP, insula, putamen, NAcc, DLPFC, caudate and primary motor cortex than slow RT trials under no drug treatment. Under placebo conditions, the fast RT trials recruited greater activation in the GP, putamen and primary motor cortex. However, the paroxetine condition showed greater activations in the fast RT trials compared to the slow RT trials only in the primary motor cortex. These results indicated paroxetine desensitized RT influence on reward-anticipation-related brain activity, meanwhile no drug and placebo conditions reflected RT influence fully or partially in the reward-related areas.

In the next step, we looked into the activation differences in the same RT (slow or fast) group among the different drug conditions. Paroxetine significantly suppressed activation in the left GP, bilateral insula, right putamen and left DLPFC as reward-anticipation-related areas compared to no drug in the fast RT trials reflecting higher motivation, not in the slow RT trials reflecting lower motivation.

In the primary motor cortex, the activation under paroxetine administration was significantly weaker than no drug in the fast RT trials only, but weaker than placebo in both fast and slow RT trials. Besides, the fast RT trials were activated greater than the slow RT trials in all three drug conditions. Thus, the characteristics shown in the reward-related areas collapsed in the primary motor cortex, although paroxetine reduced activation compared to no drug and placebo in any case.

Taken together, paroxetine attenuated the brain activity in the reward-anticipation-related areas between the subdivided RT groups and compared to no drug in the more motivated fast RT trials. When anhedonia, one of the major symptoms of MDD, is considered as decreased motivation and sensitivity to rewarding experiences, our results suggest that a single dose of paroxetine may create a relatively anhedonic state in healthy subjects.

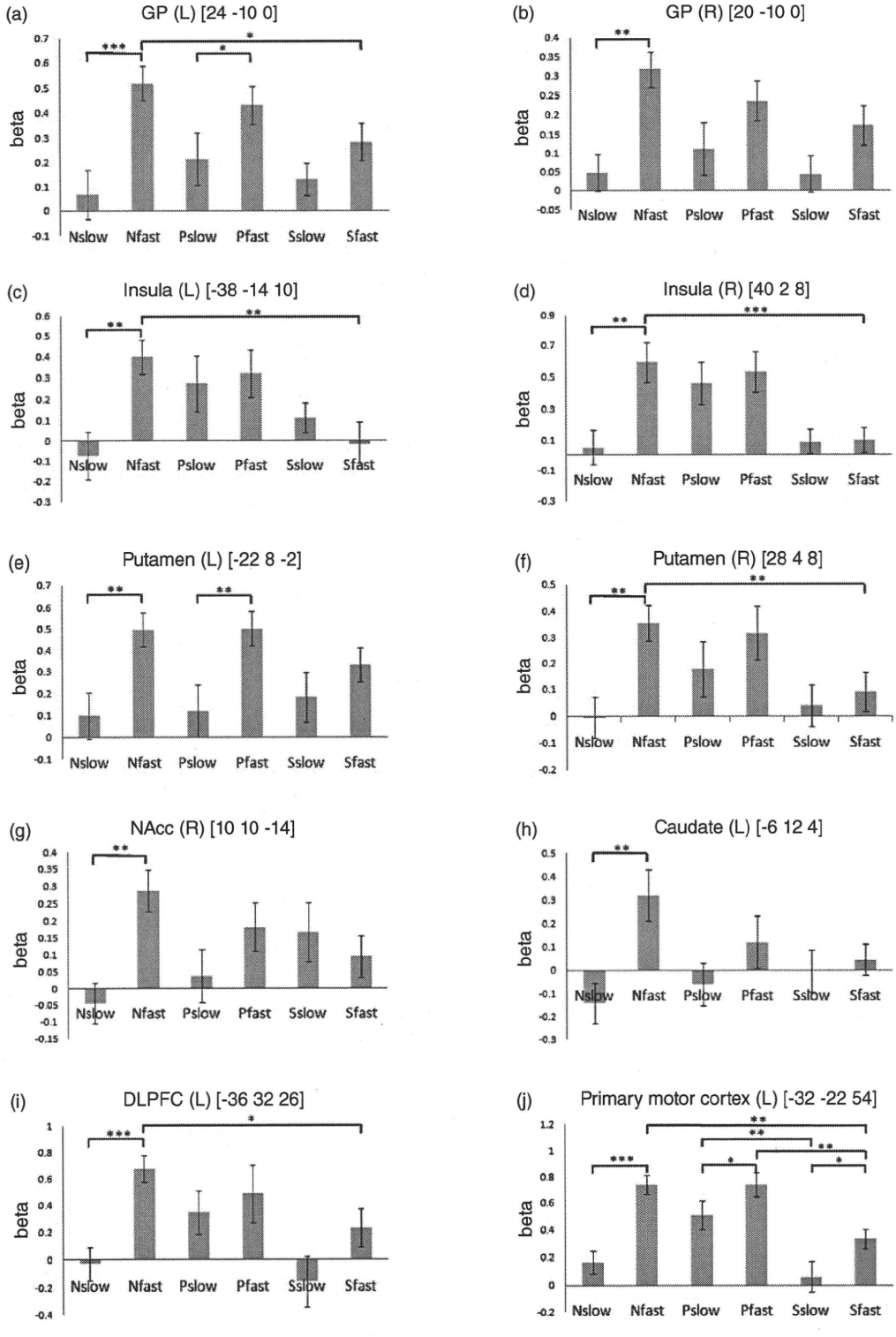

Figure 1. The mean beta values for the peak activation categorized by drug and reaction time type for the defined regions-of-interest. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$. Error bars show SEM. DLPFC, dorsolateral prefrontal cortex; GP, globus pallidus; L, left; NAcc, nucleus accumbens; R, right.

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.

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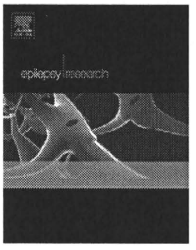

Abnormal mismatch negativity for pure-tone sounds in temporal lobe epilepsy

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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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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

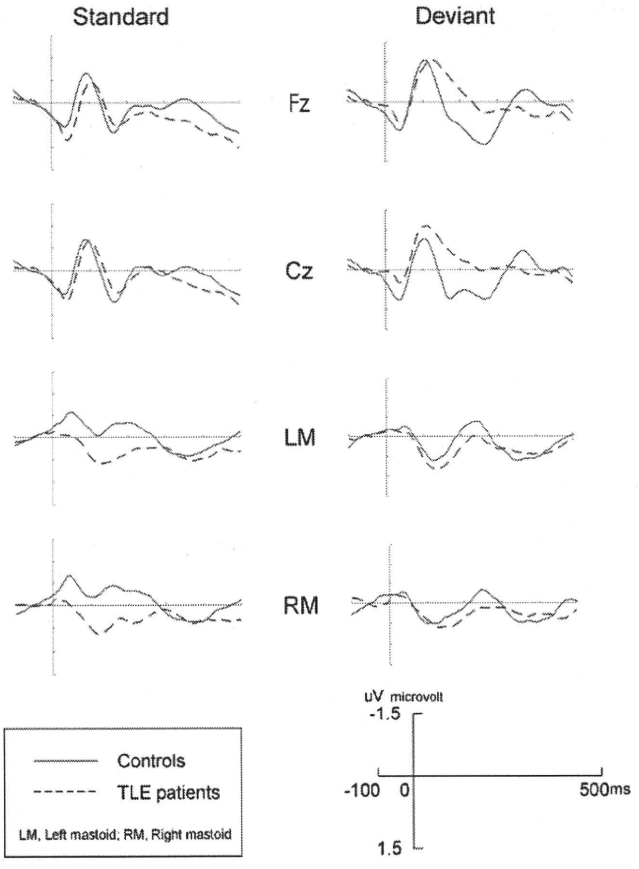

Figure 1 Comparison between grand-averaged ERPs for standard and deviant stimuli in controls and TLE patients. Solid line, control group; striped line, epilepsy group.

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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.

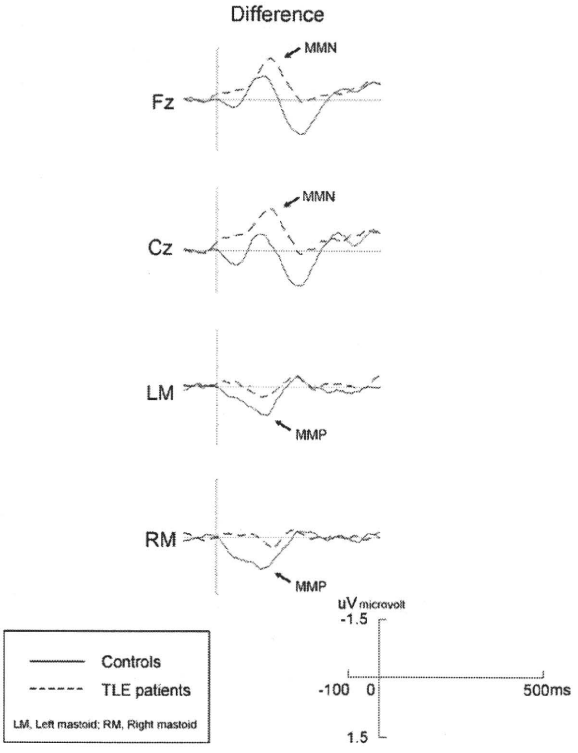

Figure 2 Deviant minus standard difference waveforms in controls and TLE patients. Solid line, control group; striped line, epilepsy group.

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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