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Changes in respiratory disorder parameters during the night in patients with obstructive sleep apnoea

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ABSTRACT

Background and objective: **Patients with OSA frequently experience cardiovascular events, especially late at night. This phenomenon raises the possibility that respiratory disorders are progressively aggravated during the course of nocturnal sleep. To test this hypothesis, we investigated the changes in respiratory disorder parameters occurring during the night in patients with OSA, in the supine position and in all sleep positions.**

Methods: **Thirty consecutive patients with OSA were enrolled in the study and categorized into those with moderate OSA ($n = 12$; AHI <40 events/h) and those with severe OSA ($n = 18$; AHI ≥40 events/h). To identify the time during the sleep period at which changes in respiratory disorder parameters were most pronounced, AHI, mean duration of apnoea and average SaO_2 were assessed during the early, middle and late segments of sleep, in the supine position and in all sleep positions.**

Results: **AHI decreased significantly with time during the course of the total sleep period, and especially during non-rapid eye movement (NREM) sleep. In the group with severe OSA, prolongation of the mean duration of apnoea and the decrease in average SaO_2 were also significant in the late segment of sleep in the supine position, especially during NREM sleep.**

Conclusions: **In patients with severe OSA, there was progressive prolongation of the mean duration of apnoea late at night and this was associated with aggravation of hypoxia in the supine position during NREM sleep. This phenomenon may contribute to the remarkable rise in blood pressure early in the morning, possibly increasing the vulnerability of these patients to cardiovascular events.**

SUMMARY AT A GLANCE

Changes in AHI, the duration of apnoea and oxygen saturation during sleep in the supine position were investigated through the nocturnal sleep course. In patients with severe OSA, the AHI decreased significantly late at night, although the duration of apnoea was prolonged and oxygen saturation decreased as the night progressed.

Key words: apnoea duration, apnoea/hypopnoea index, cardiovascular event, obstructive sleep apnoea, oxygen saturation.

INTRODUCTION

OSA is closely associated with the metabolic syndrome, which is characterized by obesity, hypertension, hyperlipidaemia and diabetes, and is a frequent complication of cardiovascular disorders.[1–5] Hypoxaemia due to OSA has been reported to trigger nocturnal angina and myocardial infarction.[6] Previous reports suggested that these complications of OSA were likely to occur during the later part of the night or early in the morning. For example, one report described the cases of two OSA patients who awoke from sleep at dawn with symptoms of minor strokes.[7] Furthermore, a previous report indicated that OSA patients have an elevated risk of sudden death due to cardiac disease while asleep between midnight and six in the morning.[8] These observations raise the question of whether the occurrence of stroke in OSA patients is attributable to the aggravation of respiratory disorders, manifested as an increase in AHI or prolongation of the mean duration of apnoea during the course of nocturnal sleep.

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Gami *et al.* reported that patients with severe OSA (AHI ≥40 events/h) had a higher risk of sudden death during sleep between midnight and six in the morning compared with those with mild-to-moderate OSA (AHI 5–39 events/h).[8] If this were the case, the changes in respiratory disorder parameters during the night in patients with OSA would appear to depend on the baseline severity of the disorder.

Some investigators have examined the changes in respiratory disorder parameters that occurred through the night in OSA patients,[9,10] but the results were not conclusive. A possible explanation is that sleeping position, which clearly influences the severity of the disorder,[11] was not taken into consideration in these studies.

To clarify whether OSA is aggravated late at night, we investigated the changes in respiratory disorder parameters occurring through the night in each of the OSA severity groups, after excluding the influence of sleeping position.

METHODS

Subjects and procedures

Consecutive eligible patients with OSA, who visited the outpatient clinic of the Japan Somnology Center between May 2003 and June 2005, and who met the following inclusion criteria were enrolled in the study: (i) fifteen or more scoreable respiratory events on nocturnal polysomnograms (n-PSGs)[12]; (ii) a periodic limb movement index (PLMI) of <5 events/h; (iii) normal heart and pulmonary function; and (iv) not taking alcohol or medications that could influence findings on the night of PSG recording. In addition, patients who had both a period of rapid eye movement (REM) sleep and a period of sleep in the supine position during each of the three sleep segments were enrolled in the study. Similar to the study of Gami *et al.*,[8] patients were categorized into two groups: those with moderate OSA (AHI <40 events/h) and those with severe OSA (AHI ≥40 events/h). A total of 30 patients with OSA were enrolled in the study (12 with moderate OSA, 18 with severe OSA; 24 men, 6 women; mean age 35.8 ± 4.0 years; mean BMI 30.5 ± 6.8 kg/m^2; mean AHI 56.9 ± 32.9 events/h; mean duration of apnoea 26.1 ± 8.5 s; mean average SaO_2 90.6 ± 5.6%). The ethics committee of the Neuropsychiatric Research Institute approved this retrospective study and written informed consent was obtained from all participants.

Diagnostic PSG recordings and measurements, including four-channel scalp electroencephalogram (EEG) (C3/A2, C4/A1, O1/A2, O2/A1), two electrooculograms, submental electromyogram, ECG, nasal/oral airflow, SaO_2, snoring sounds, chest/abdominal respiratory effort and anterior tibialis electromyogram, were obtained using an Alice4 system (Respironics Inc., Murrysville, PA, USA).

Sleep stages were scored according to the criteria of Rechtschaffen and Kales,[13] and EEG arousal and PLMI were evaluated according to the criteria of the American Sleep Disorders Association.[14,15] Respiratory events were also assessed according to the diagnostic criteria of the American Academy of Sleep Medicine Task Force.[16]

The sleep period time (SPT) on n-PSG was divided into three sub-periods of equal length (early segment, middle segment, late segment).[9] Respiratory disorder parameters, including AHI, mean duration of apnoea and average SaO_2, were evaluated in the supine position and in all sleep positions (supine and non-supine positions). These parameters were also assessed during non-rapid eye movement (NREM) sleep and REM sleep. The data for the three sleep period segments were compared. Five patients in the severe OSA group, who did not have a period of REM sleep in the supine position in at least one of the three sleep period segments were excluded from the analysis of the data for the REM sleep period.

Statistical analyses

The assumption that the data were normally distributed was verified using the Shapiro–Wilk test, and Levene's test was also used to verify the homogeneity of variances. Patient characteristics, respiratory disorder parameters and sleep stage-related variables for the two severity groups were compared using Student's *t*-test. Paired *t*-tests were used for comparisons of respiratory disorder parameters during NREM sleep or REM sleep, and during sleep in the supine position or all sleep positions. The proportions of the sleep period spent in the supine position relative to that spent in all sleep positions, during NREM sleep and REM sleep, were also analysed by one-way repeated measures analysis of variance (ANOVA). The respiratory disorder parameters measure during the three sleep segments were analysed by two-way repeated measures ANOVA, with one independent factor (moderate OSA or severe OSA) and one repeated measure (early segment, middle segment, late segment), in the supine position and in all sleep positions. For each of the two severity groups, the respiratory disorder parameters measured during the respective sleep segments were analysed by two-way repeated measures ANOVA, with one independent factor (supine position or all sleep positions) and one repeated measure (each sleep segment). When significant differences were identified by ANOVA, a Bonferroni post-hoc analysis was performed. Significance was inferred for $P < 0.05$. Statistical analyses were performed using SPSS version 11.5J 2002 software (SPSS Inc., Tokyo, Japan).

RESULTS

Physical characteristics, respiratory disorder parameters and sleep-related parameters

Table 1 shows the physical characteristics of the patients, as well as respiratory disorder parameters, and the other sleep-related parameters for the two patient groups.

Table 1 Physical characteristics, respiratory disorder parameters and sleep-related variables in patients with OSA

	All patients ($n = 30$)	Patients with moderate OSA ($n = 12$)	Patients with severe OSA ($n = 18$)
Male/female	26/4	10/2	16/2
Age, years	35.8 ± 4.0	35.4 ± 3.2	36.1 ± 4.5
BMI, kg/m^2	30.5 ± 6.8	27.1 ± 5.0	32.7 ± 7.1*
AHI, events/h	56.9 ± 32.9	27.2 ± 5.0	76.8 ± 28.0**
Index of central apnoea	0.4 ± 0.4	0.5 ± 0.4	0.3 ± 0.4
Index of mixed apnoea	1.1 ± 2.6	0.0 ± 0.0	1.9 ± 3.2*
Mean duration of apnoea, s	26.1 ± 8.5	23.1 ± 8.6	28.0 ± 7.8**
Average SaO_2, %	90.6 ± 5.6	94.6 ± 1.4	87.9 ± 5.7**
SPT, min	539.4 ± 36.7	533.5 ± 36.0	543.3 ± 37.6
TST, min	498.9 ± 42.9	500.0 ± 45.9	498.1 ± 42.1
WASO, %SPT	7.5 ± 4.6	6.3 ± 5.0	8.3 ± 4.3
Stage 1 sleep, %SPT	31.2 ± 16.2	18.6 ± 8.6	39.6 ± 14.6**
Stage 2 sleep, %SPT	39.5 ± 14.1	47.5 ± 10.6	34.1 ± 13.8**
SWS, %SPT	3.8 ± 4.6	5.3 ± 4.9	2.8 ± 4.3
REM stage, %SPT	18.1 ± 5.5	22.4 ± 5.2	15.2 ± 3.6**
Sleep efficiency, %	92.5 ± 4.6	93.7 ± 5.0	91.7 ± 4.3
Proportion of SPT spent in the supine position, %	88.2 ± 12.4	89.7 ± 11.3	87.1 ± 13.3

Values are mean ± SD unless otherwise indicated.
*$P < 0.05$, **$P < 0.01$ compared with the moderate OSA group by Student's *t*-test.
REM, rapid eye movement; SPT, sleep period time; SWS, slow wave sleep; WASO, wake after sleep onset.

The patients with severe OSA had a significantly higher BMI ($P < 0.05$), higher AHI ($P < 0.01$), lower average SaO_2 during sleep ($P < 0.01$) and longer mean duration of apnoea ($P < 0.01$) compared with the patients with moderate OSA. With regard to sleep-related variables, the severe OSA group showed a significantly higher proportion of stage 1 sleep ($P < 0.01$) and a lower proportion of stage 2 sleep ($P < 0.01$), as well as a lower proportion of REM sleep ($P < 0.01$). In fact, 13 patients did not sleep in the lateral position at all, and only seven patients slept in the lateral position during all three sleep segments. There was no significant difference in the proportion of SPT in the supine position between the two subject groups.

Comparison of respiratory disorder parameters during NREM and REM sleep

Table 2 shows the differences in respiratory disorder parameters between the NREM and REM sleep periods. In the moderate OSA group, the AHI was significantly higher ($P < 0.01$), the mean duration of apnoea was significantly longer ($P < 0.05$), and the average SaO_2 was significantly lower ($P < 0.01$) during REM sleep compared with NREM sleep. In the severe OSA group, the mean duration of apnoea was significantly longer during REM sleep than during NREM sleep ($P < 0.01$). Furthermore, average SaO_2 was significantly lower during REM sleep than during NREM sleep ($P < 0.01$). However, in the severe OSA group, the AHI was significantly lower during REM sleep than during NREM sleep ($P < 0.05$).

Table 2 Respiratory disorder parameters during NREM and REM sleep periods in patients with moderate or severe OSA

	NREM sleep period	REM sleep period
Moderate OSA group ($n = 12$)		
AHI, events/h	22.9 ± 7.7	45.2 ± 14.3**
Mean duration of apnoea, s	20.9 ± 8.7	24.5 ± 11.3*
Average SaO_2, %	95.2 ± 1.3	92.6 ± 2.0**
Severe OSA group ($n = 18$)		
AHI, events/h	81.3 ± 26.8	72.5 ± 19.8*
Mean duration of apnoea, s	27.3 ± 7.9	33.6 ± 9.5**
Average SaO_2, %	88.6 ± 5.2	84.1 ± 9.1**

Values are mean ± SD.
*$P < 0.05$, **$P < 0.01$ compared with NREM sleep period by paired *t*-test.
NREM, non-rapid eye movement; REM, rapid eye movement.

Respiratory disorder parameters in the supine position compared with all sleep positions

Table 3 shows the differences in respiratory disorder parameters according to sleep period in the supine position and all sleep positions. In the moderate OSA group, the mean duration of apnoea was significantly longer ($P < 0.01$) and SaO_2 was significantly lower ($P < 0.01$) during sleep in the supine position compared with all sleep positions. In the severe OSA group, the AHI was significantly higher ($P < 0.05$), the

mean duration of apnoea was significantly longer ($P < 0.05$), and SaO_2 was significantly lower ($P < 0.05$) during sleep in the supine position compared with all sleep positions.

Proportions of sleep in the supine position relative to all sleep positions during each sleep segment

In the moderate OSA group, there was no significant difference in the proportions of sleep in the supine position relative to all sleep positions among the three sleep segments, either during NREM sleep or REM sleep. However, in the severe OSA group, there were significant differences in the proportions of sleep in the supine position among the three sleep segments, both during NREM sleep and REM sleep ($P < 0.05$). Post-hoc tests showed that the proportions of sleep in the supine position during the middle and late segments of sleep were significantly lower than those in the early segment, both during the NREM and REM sleep periods ($P < 0.05$) (Table 4).

Table 3 Respiratory disorder parameters measured during sleep in the supine position and during sleep in all positions

	Supine position ($n = 30$)	All positions† ($n = 30$)
Moderate OSA group ($n = 12$)		
AHI, events/h	27.5 ± 5.0	27.0 ± 5.1
Mean duration of apnoea, s	22.9 ± 8.4*	22.1 ± 8.4
Average SaO_2, %	93.9 ± 1.3*	95.1 ± 1.1
Severe OSA group ($n = 18$)		
AHI, events/h	79.9 ± 26.2**	77.1 ± 28.0
Mean duration of apnoea, s	28.0 ± 7.7**	26.9 ± 7.1
Average SaO_2, %	88.0 ± 5.9**	88.4 ± 6.0

Values are mean ± SD.

*$P < 0.01$, **$P < 0.05$ compared with all sleep positions overall.

†Supine and lateral positions.

Changes in AHI through the night

With respect to changes in AHI, there were no significant interactions among the severity groups, sleep segments and sleep in the supine position or all sleep positions, or between sleep positions and sleep segments in either the moderate or severe OSA groups for any sleep period.

During sleep in either the supine position or all sleep positions, the AHI was significantly lower in the middle and late segments than in the early segment of the total sleep period, and also for the NREM sleep period ($P < 0.01$ for both) (Fig. 1a,b). For the REM sleep period, there were no significant differences among the sleep segments for any sleeping position (Fig. 1c).

In the severe OSA group, the AHI was significantly lower in the middle and late segments than in the early segment, both for the total sleep period and the NREM sleep period ($P < 0.01$ for both) (Fig. 1a,b). This trend was not observed for the REM sleep period (Fig. 1c). In the moderate OSA group, there were no significant differences in the AHI among the sleep segments for any sleep period.

Changes in the mean duration of apnoea through the night

With respect to changes in the mean duration of apnoea, the interaction between severity groups and sleep segments was significant for the total sleep period and for NREM sleep in the supine position and all sleep positions ($P < 0.05$ for all). For the total sleep period in the severe OSA group, the mean durations of apnoea in the middle and late segments were significantly longer than in the early segment, in both the supine position and all sleep positions ($P < 0.01$ for both) (Fig. 2a). During the NREM sleep period in the severe OSA group, the mean duration of apnoea was significantly longer in the late segment than in either the early or middle segments in the supine position ($P < 0.01$), and it was also significantly longer in the late segment than in the early segment ($P < 0.01$) or middle segment ($P < 0.05$) in all sleep positions (Fig. 2b). For the REM sleep period, there were no significant differences in the mean durations of

Table 4 Proportion of the total sleep period spent in the supine position as a percentage of time spent in all sleep positions during each segment of sleep

	Early segment	Middle segment	Late segment
Moderate OSA group ($n = 12$)			
NREM sleep period	94.5 ± 12.2	91.0 ± 11.9	88.7 ± 14.9
REM sleep period	90.9 ± 30.2	83.1 ± 33.2	81.4 ± 25.2
Severe OSA group ($n = 18$)			
NREM sleep period	94.4 ± 12.5	86.1 ± 20.2*	86.4 ± 18.1*
REM sleep period	99.9 ± 0.1	78.8 ± 32.9*	72.8 ± 33.9*

Values are mean ± SD percentages.

*$P < 0.05$ compared with early segment.

NREM, non-rapid eye movement; REM, rapid eye movement.

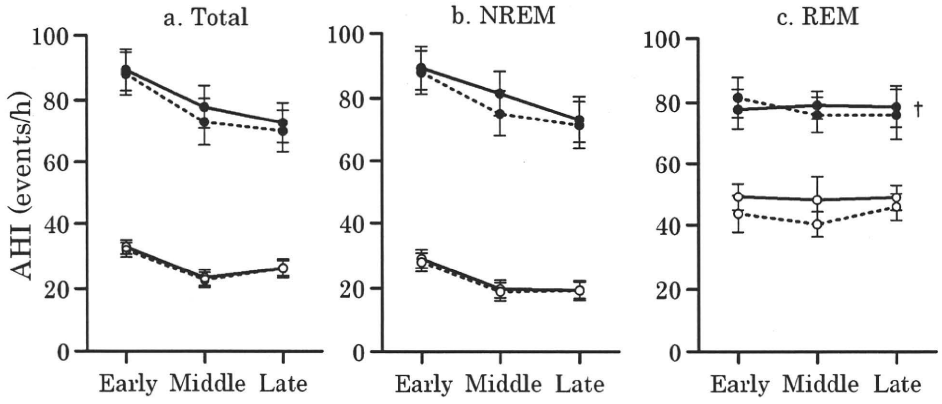

Figure 1 Changes in AHI through the night. (a) The severity group × sleep segment interactions in the supine position and in all sleep positions were not significant. For the main effect of severity group in the supine position, $F_{1,28} = 42.214$, $P < 0.01$, and for all sleep positions, $F_{1,28} = 37.198$, $P < 0.01$. For the main effect of sleep segment in the supine position, $F_{2,56} = 12.989$, $P < 0.01$, and for all sleep positions, $F_{2,56} = 12.729$, $P < 0.01$. The main effects of sleep position and the sleep position × sleep segment interactions were not significant in the moderate and severe OSA groups. For the main effect of sleep segment in the severe OSA group, $F_{2,34} = 24.319$, $P < 0.01$, and in the moderate OSA group it was not significant. (b) The severity group × sleep segment interactions in the supine position and in all sleep positions were not significant. For the main effect of severity group in the supine position, $F_{1,28} = 52.632$, $P < 0.01$, and for all sleep positions, $F_{1,28} = 43.299$, $P < 0.01$. For the main effect of sleep segment in the supine position, $F_{2,56} = 9.806$, $P < 0.01$, and for all sleep positions, $F_{2,56} = 14.437$, $P < 0.01$. The main effects of sleep position and the sleep position × sleep segment interactions were not significant in the moderate and severe OSA groups. For the main effect of sleep segment in the severe OSA group, $F_{2,34} = 17.036$, $P < 0.01$, and in the moderate OSA group it was not significant. (c) The severity group × sleep segment interactions in the supine position and in all sleep positions were not significant. For the main effect of severity group in the supine position, $F_{1,28} = 22.147$, $P < 0.01$, and for all sleep positions, $F_{1,23} = 20.444$, $P < 0.01$. The main effects of sleep segment in the supine position and in all sleep positions were not significant. The main effects of sleep position, sleep segment, and the sleep position × sleep segment interactions were not significant in the moderate and severe OSA groups. NREM, non-rapid eye movement; REM, rapid eye movement. Circles indicate mean values and error bars indicate SEM. †$n = 13$, after exclusion of five patients who had no REM sleep period in the supine position during any of the three sleep segments. (–○–) moderate, supine position, (–●–) severe, supine position, (··○··) moderate, sleep positions overall, (··●··) severe, sleep positions overall.

apnoea among the sleep segments, sleep positions and severity groups (Fig. 2c).

Changes in average SaO_2 through the night

The average SaO_2 was significantly lower in the middle segment than in the early segment ($P < 0.01$), and average SaO_2 in the late segment was also significantly lower than that in either the early or middle segments in the supine position for the total sleep period ($P < 0.01$) (Fig. 3a). For the NREM sleep period, the interaction between the severity groups and sleep segments was significant only for the supine position ($P < 0.05$). The average SaO_2 values in the middle and late segments were significantly lower than that in the early segment in the severe OSA group in the supine position ($P < 0.01$) (Fig. 3b). However, there was no such trend in the moderate OSA group. For the REM sleep period, there were no significant differences in the average SaO_2 among the sleep segments, sleep positions and severity groups (Fig. 3c).

In the severe OSA group, the interaction between sleep positions and sleep segments was significant only for the NREM sleep period ($P < 0.05$). In this patient group, average SaO_2 values in the middle and late segments were significantly lower than that in the early segment in the supine position ($P < 0.05$) (Fig. 3b). In the moderate OSA group, there were no significant differences in average SaO_2 values among the segments.

DISCUSSION

Previous studies investigating the changes in AHI or duration of apnoea through the course of nocturnal sleep did not take the sleeping position into consideration, although this clearly influences the severity of OSA.[9–11] Consistent with previous studies,[11] the present study showed that the AHI was higher during sleep in the supine position than in all sleep positions. Considering that there was no significant difference in the proportions of SPT in the supine position between the two severity groups, the AHI in these patients was not likely to have been influenced by their sleeping position. However, 13 patients had no SPT in the lateral position and only seven patients had sleep periods in the lateral position in all three sleep segments. Therefore, in the present study, the changes in respiratory disorder parameters in the supine position were compared with those in all sleep positions.

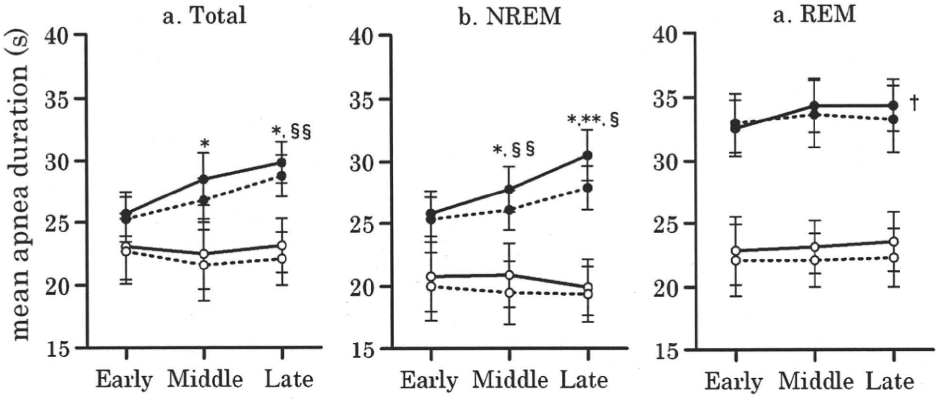

Figure 2 Changes in the mean duration of apnoea through the night. (a) For the severity group × sleep segment interaction in the supine position, $F_{2,56} = 4.486$, $P < 0.05$, and for all sleep positions, $F_{2,56} = 3.795$, $P < 0.05$. The main effects of severity group in the supine position and in all sleep positions were not significant. For the main effect of sleep segment in the supine position, $F_{2,56} = 4.201$, $P < 0.05$, and for all sleep positions it was not significant. The main effects of sleep position and the sleep position × sleep segment interactions were not significant in the moderate and severe OSA groups. For the main effect of sleep segment in the severe OSA group, $F_{2,34} = 20.926$, $P < 0.01$, and in the moderate OSA group it was not significant. (b) For the severity group × sleep segment interaction in the supine position, $F_{2,56} = 9.544$, $P < 0.01$, and for all sleep positions, $F_{2,56} = 4.497$, $P < 0.05$. For the main effect of severity group in the supine position, $F_{1,28} = 6.225$, $P < 0.05$, and for all sleep positions, $F_{1,28} = 6.464$, $P < 0.05$. For the main effect of sleep segment in the supine position, $F_{2,56} = 4.423$, $P < 0.05$, and for all sleep positions it was not significant. The main effects of sleep position and the sleep position × sleep segment interactions were not significant in the moderate and severe OSA groups. For the main effect of sleep segment in the severe OSA group, $F_{2,34} = 25.127$, $P < 0.01$, and in the moderate OSA group it was not significant. (c) The severity group × sleep segment interactions in the supine position and in all sleep positions were not significant. For the main effect of severity group in the supine position, $F_{1,28} = 12.016$, $P < 0.01$, and for all sleep positions, $F_{1,23} = 9.298$, $P < 0.01$. The main effects of sleep segment in the supine position and in all sleep positions were not significant. The main effects of sleep position, sleep segment and the sleep position × sleep segment interactions were not significant in the moderate and severe OSA groups. $*P < 0.01$ compared with the early segment; $**P < 0.05$ compared with the middle segment; §$P < 0.01$ compared with the moderate OSA group; §§$P < 0.05$ compared with the moderate OSA group. Circles indicate mean values and error bars indicate SEM. †$n = 13$, after exclusion of five patients who had no REM sleep period in the supine position during any of the three sleep segments. NREM, non-rapid eye movement; REM, rapid eye movement. (–○–) moderate, supine position, (–●–) severe, supine position, (··○··) moderate, sleep positions overall, (··●··) severe, sleep positions overall.

In agreement with the results of some previous studies,[9,10] there was a prolongation of the duration of apnoea in the total sleep period and NREM sleep period, specifically in the patients with severe OSA. In this patient group, this trend was apparent both in the supine position and in all sleep positions. However, the trend for prolongation of duration of apnoea was smaller for all sleep positions than for the supine position. This finding may be ascribed to the lower proportion of sleep spent in the supine position, and the duration of apnoea being significantly longer than in all sleep positions, in the latter part of the night.

In attempting to explain the prolongation of apnoea in the latter part of the night, the following factors should be considered. First, chemosensitivity to hypercapnia is reported to be regulated by circadian rhythm,[17,18] and responsiveness to hypercapnia declines from a maximum at 1800 h to a minimum at about 0600 h.[17] Thus, the decline in responsiveness to hypercapnia may be manifested as a delay in the termination of apnoeic events. Second, repetitive apnoea through the night may result in an increase in the arousal threshold and/or a decrease in the strength of the upper airway dilator muscle.[10,19] Third, the surface tension of the fluid lining the upper airway mucosa may increase as the night progresses, possibly due to repetitive opening of the mouth, associated with apnoeic events, and/or decreased salivary flow due to circadian variation.[20–22]

An earlier report indicated that the AHI increased significantly in the latter part of the night, especially in patients with the most severe OSA (AHI ≥85 events/h).[10] In contrast, the present study showed a significant decrease in AHI in the late sleep segment for the patients with severe OSA. The reason for this discrepancy is unclear. However, the decline in chemosensitivity described previously may suppress the occurrence of apnoeic events during wake–sleep transition in the latter part of the night.[23] Another explanation is that the prolongation of apnoeic episodes during this sleep period may result in a decreased frequency of such episodes.

A previous study showed that neither pre-apnoeic nor end-apnoeic oxygen saturation was significantly different among the quartiles of the total sleep period, or during the NREM or REM sleep periods.[10] However, the present results indicated that there was a gradual decline in average SaO_2 during the NREM sleep period

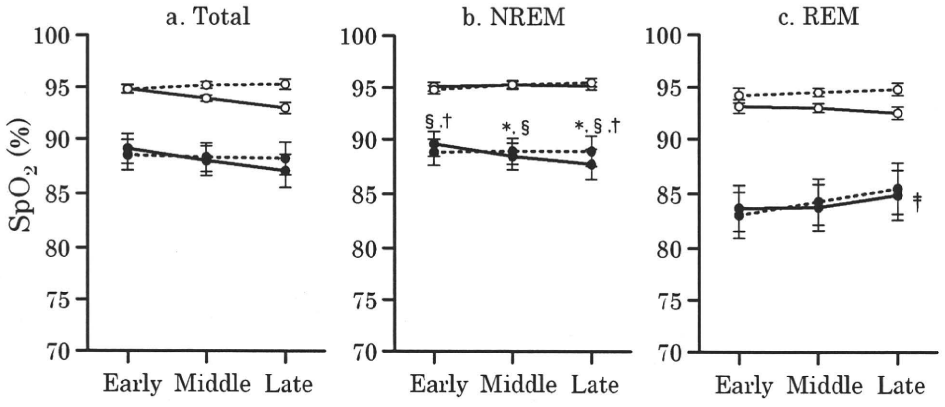

Figure 3 Changes in average SaO_2 through the night. (a) The severity group × sleep segment interactions in the supine position and in all sleep positions were not significant. For the main effect of severity group in the supine position, $F_{1,28} = 11.382$, $P < 0.01$, and for all sleep positions, $F_{1,28} = 14.832$, $P < 0.01$. For the main effect of sleep segment in the supine position, $F_{2,56} = 21.863$, $P < 0.01$, and for all sleep positions it was not significant. The main effects of sleep position, sleep segment, and the sleep position × sleep segment interactions were not significant in the moderate and severe OSA groups. (b) For the severity group × sleep segment interaction in the supine position, $F_{2,56} = 4.728$, $P < 0.05$, and for all sleep positions it was not significant. For the main effect of severity group in the supine position, $F_{1,28} = 18.433$, $P < 0.01$, and for all sleep positions, $F_{1,28} = 15.416$, $P < 0.01$. For the main effect of sleep segment in the supine position, $F_{2,56} = 5.243$, $P < 0.01$, and for all sleep positions it was not significant. The main effects of sleep position, sleep segment, and the sleep position × sleep segment interactions were not significant in the moderate and severe OSA groups. (c) The severity group × sleep segment interactions in the supine position and in all sleep positions were not significant. For the main effect of severity group in the supine position, $F_{1,28} = 13.701$, $P < 0.01$, and for all sleep positions, $F_{1,24} = 12.998$, $P < 0.01$. The main effects of sleep segment in the supine position and in all sleep positions were not significant. The main effects of sleep position, sleep segment, and the sleep position × sleep segment interactions were not significant in the moderate and severe OSA groups. *$P < 0.01$ compared with the early segment; §$P < 0.01$ compared with the moderate OSA group; †$P < 0.05$ compared with all sleep positions. ‡$n = 13$, after exclusion of five patients who had no REM sleep period in the supine position during any of the three sleep segments. NREM, non-rapid eye movement; REM, rapid eye movement; Circles indicate mean values and error bars indicate SEM. (–○–) moderate, supine position, (–●–) severe, supine position, (··○··) moderate, sleep positions overall, (··●··) severe, sleep positions overall.

in patients with severe OSA, probably due to the prolongation of apnoea. In this patient group, there was no sleep course-dependent change in average SaO_2 in all sleep positions. This difference may arise from the reduced prolongation of the duration of apnoea in these positions compared with the supine position. Consequently, the present results suggest that changes in SaO_2 through the course of sleep depend on the duration of sleep in the supine position in the respective sleep segments. Kishimoto *et al.* reported that mean nocturnal SaO_2 was inversely correlated with both diastolic and systolic morning blood pressures.[24] A lowering of mean SaO_2 may contribute to the elevation of sympathetic nervous activity leading to increased systemic blood pressure. This phenomenon may act cooperatively with progressive prolongation of the REM sleep period, during which respiratory disorder is aggravated and sympathetic nervous activity is increased, to exacerbate the elevation of blood pressure in the early morning, and possibly increase the likelihood of cardiovascular events in the late segment of nocturnal sleep, especially in patients with severe OSA.[25–28]

This study had some limitations. First, it was performed on a small number of patients with OSA, who may not be representative of OSA patients in general. Moreover, the patients included in the study were restricted to an age range of 30–40 years. Various factors, including increased collapsibility of the pharyngeal airway during sleep,[29] instability of sleep states,[30] fluctuations in upper airway resistance,[31] and reduced loop gain,[32] have been reported to affect the severity of sleep-disordered breathing in elderly patients with OSA. For this reason, younger patients with OSA were specifically recruited for this study so that the changes in OSA could be investigated under homogeneous conditions. To clarify the relationship between the occurrence of nocturnal strokes and OSA in elderly patients,[33] a further study of similar design but including elderly OSA patients, is required. Second, this retrospective study did not clarify the relationship between aggravation of the respiratory disorder and increased vulnerability to cardiovascular events in the latter part of the night. A prospective follow-up study is required to investigate whether there is a causal relationship. Third, the influence of central and/or mixed apnoea on the changes in the measured respiratory disorder parameters could not be investigated because of the small numbers of patients with these types of apnoea. Further studies should investigate changes in these types of apnoea because such events are closely associated with

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 ($r=0.64$, $P<0.0005$).

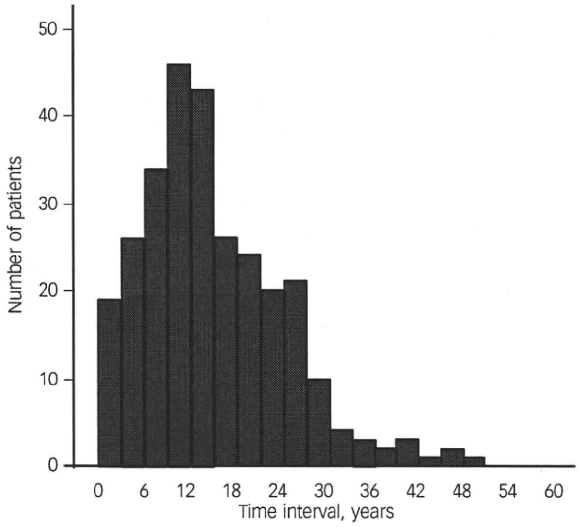

Fig. 1 Distribution of the time intervals (years) between the onset of epilepsy and that of interictal psychosis (mean 14.4 years, s.d. = 9.2, range 0–51, median 13).

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.

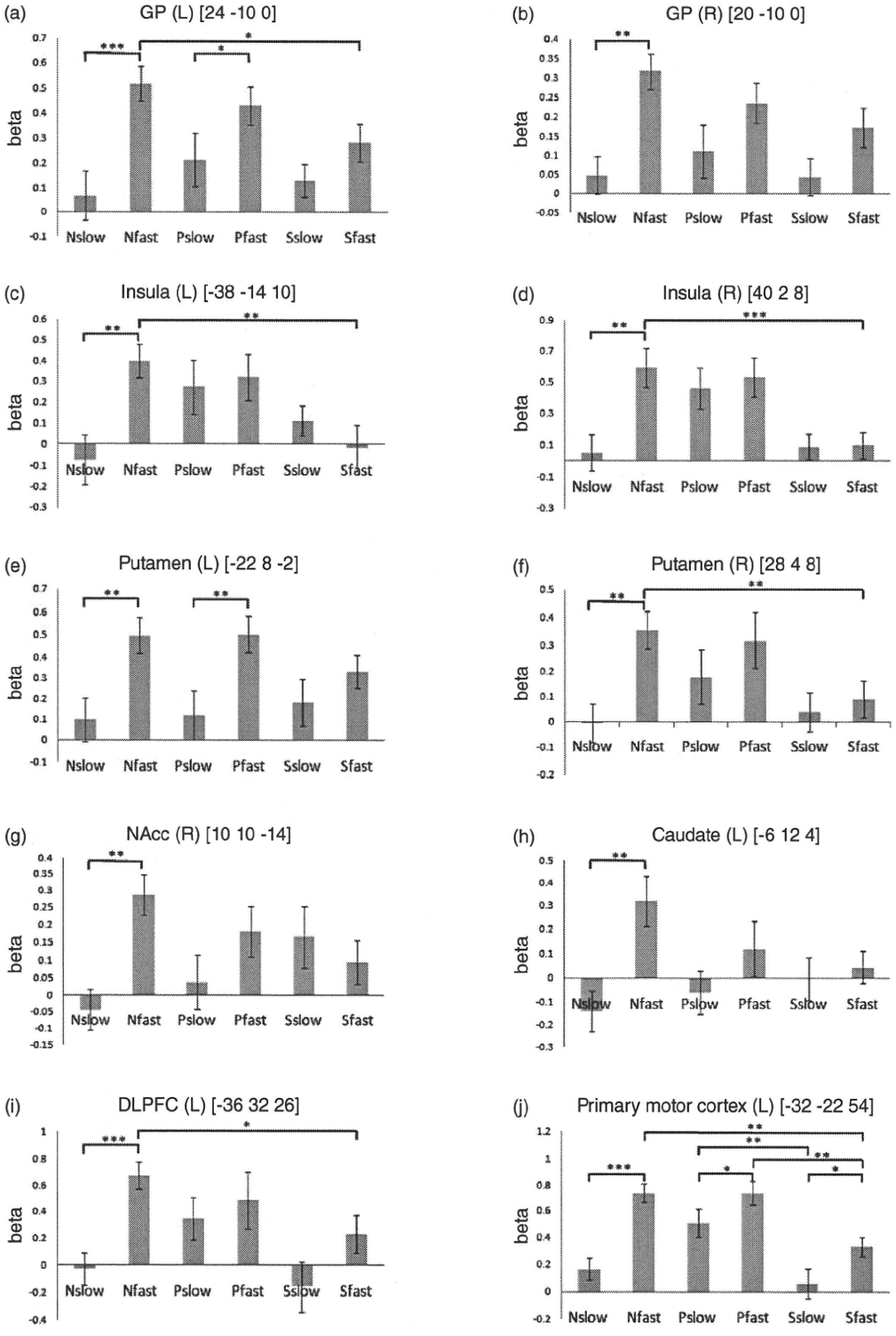

Figure 1. The mean beta values for the peak activation categorized by drug and reaction time type for the defined regions-of-interest. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$. Error bars show SEM. DLPFC, dorsolateral prefrontal cortex; GP, globus pallidus; L, left; NAcc, nucleus accumbens; R, right.

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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