after completion of the infusion. The rats were then grouped into four to six in a cage with free access to food and water, under a cycle of 12 h of light (0700–1900 hrs) and 12 h of dark.

On the 28th postoperative day, the rats were anesthetized with pentobarbital sodium (40 mg/kg, i.p.) and mounted on a stereotaxic apparatus. Microdialysis probes (10,000 MW cutoff, AN 69 Filtral 16, Hospal, Uden, The Netherlands) were implanted into the left NAC or BLA according to the atlas of Paxinos and Watson (Paxinos and Watson, 1998). The exposed tip length of the probe membrane was 1.5 mm (i.d., 220 μm; o.d., 310 μm). Coordinates of the tip were A 1.2 mm, L 1.2 mm, and V 8.0 mm from bregma for the NAC, and A 2.8 mm, L 5.2 mm, V 9.6 mm for the BLA. A guide cannula (23-gauge stainless steel cannulae, 20 mm long) for microinjection to the left mPFC was positioned using the following coordinates: A 3.2 mm, L 0.6 mm, V 3.7 mm from bregma. Microdialysis probe and guide cannula were secured with skull screws and dental acrylate. Following surgery, the rats were housed in individual cages with free access to food and water.

Microinjection of lidocaine

Lidocaine, in a volume of 0.5 μl, was injected into the left mPFC via injection cannula (30-gauge stainless steel cannulae, 35 mm long) that were lowered through the hollow implanted guide cannula. Injection cannula projected 1.5 mm beyond the tip of the guide cannula. Lidocaine (40 mg/ml, Sigma-Aldrich) was dissolved in artificial cerebrospinal fluid (CSF) (NaCl, 147 mM; KCl, 3.0 mM; $CaCl_2$, 1.2 mM; $MgSO_4$, 1.2 mM, and NaH_2PO_4, 0.4 mM at pH 7.40), which served as the treatment vehicle. Microinjections were performed using a Model PHD 2000 infusion pump (Harvard Apparatus, MA) at the rate of 0.2 μl/min. The injection cannulae were left in place for an additional 5 min after completion of the infusion.

Microdialysis procedures

MAP (1.0 mg/kg, i.p.)-induced extracellular DA release in the NAC and BLA was measured using microdialysis technique based on our previous reports (Uehara et al., 2000, 2003, 2004). The dialysis experiment was carried out 24–48 h after surgery on freely moving rats. Animals were brought to the testing room in their home cages and immediately placed in an ambulation observation chamber as described below. For habituation, microdialysis experiment was started at least 2 h after placement of rats to the test chamber. Artificial CSF (described above) was pumped through the probe at a rate of 2.0 μl/min with a Model 22 microdialysis pump (Harvard Apparatus, MA). Each probe attached to the head of a rat was connected by teflon tubing to a Model AS-10 autoinjector (Eicom, Kyoto, Japan) of a high-performance liquid chromatography (HPLC)-ECD system, and perfusate was injected automatically into the apparatus every 20 min. The Coulochem II Electrochemical Detection System (ESA, Bedford, MA) and an acetate–citrate buffer (pH 4.1) were used in this study. The minimum detectable level of DA was 0.1 pg/injection.

MAP (methamphetamine hydrochloride injection, 3.0 mg/ml; Dainippon Sumitomo Pharmaceuticals, Tokyo, Japan) was injected i.p. to avoid stress effects associated with systemic administration of MAP, an indwelling i.p. catheter was placed when the probe was implanted. Microinjection of lidocaine or artificial CSF into the left mPFC was started 20 min before the MAP administration.

Locomotor activity

Locomotor activity was measured during the microdialysis experiment according to a previous report (Sumiyoshi et al., 2004), with an ambulation observation chamber (blackened vinyl chloride cages, 40 cm × 40 cm × 40 cm; AMB-3001, OHara & Co., Ltd., Tokyo, Japan) equipped with 6 × 6 photoelectric light sources spaced at 7-cm intervals and 2.5 cm above the floor (AMB-2020, OHara & Co., Ltd.). Interruptions of light beams were registered as activity counts, and were summarized every 5 min by the Logger interface control system (IF-10-LOG, OHara & Co., Ltd.). MAP-induced locomotor activity was recorded for 3 h after the administration of MAP. The dose of MAP was chosen based on the previous report (Sumiyoshi et al., 2004) that demonstrate a significant effect of the left EC on MAP-induced locomotion in rats.

Apparatus and procedure of PPI

All testing occurred within startle chambers (Ohara & Co., Ltd.), which were housed in a sound-attenuated room with a 60 dB ambient noise level. Each startle chamber consisted of a Plexiglas cylinder 9.4 cm in internal diameter resting on an 11 cm × 22 cm Plexiglas stand. Acoustic stimuli and background noise were given via speakers mounted 12.2 cm above the Plexiglas cylinders, controlled with a computer box (Ohara & Co., Ltd.). A piezoelectric device mounted below the Plexiglas stand detected and transduced motion within the cylinder.

Fifteen minutes after receiving the injection of lidocaine or artificial CSF into the left mPFC, rats were placed in a startle chamber. Five minutes after the acclimation period, they were exposed to six blocks of four different stimulus types, i.e., pulse-alone; 40 ms 120 dB white noise bursts: prepulse–pulse; 20 ms, white noise pulse of 74, 78 dB followed by 20 ms 120 dB white noise pulse at a fixed interstimulus interval (ISI) of 100 ms. Trials were presented in randomized order, with 20, 25, and 30 s randomized interval.

Histology

After each experiment, all rats were deeply anesthetized with pentobarbital sodium and were sacrificed by decapitation. Coronal sections were prepared from the brain including the EC, and were stained with cresyl violet. The location of the dialysis probe and microinjection cannulae were verified by dissection of the brain.

Presentation of the results and statistics

Data were analyzed by analysis of variance (ANOVA) using SPSS software (version 12.0J for windows, SPSS). DA levels in the dialysates are expressed as picogram/40 μl. The DA data are calculated by subtracting the basal DA levels (the mean of three consecutive samples before microinjection of lidocaine or artificial CSF) from DA concentrations at each time point. Basal concentrations of DA in the dialysate were compared by one-way ANOVA with operation status (Status = sham, lesion) as between-group factor. Data from challenge experiments were analyzed using three-way repeated measures ANOVA. Microinjection status (Injection; lidocaine, CSF) and operation status (Operation; sham, lesion) were treated as between-group variable, and time as repeated measures variable. For comparisons of tonic DA release in each operation status, two-way repeated ANOVA was performed with injection as between-group variable, and time as repeated measures variable.

For comparisons of locomotor activity, two-way ANOVA was performed with injection and operation as between-subject factor. Since our a priori hypothesis predicted a difference between the two microinjection condition (lidocaine, CSF), subsequent one-way ANOVA was performed with operation as a between-subject factor in each microinjection status.

PPI data were presented as the percentage of PPI (%PPI), which was calculated using the following formula: %PPI = 100 − [(SA for prepulse-pulse trials)/(SA for pulse-alone trials)] × 100. Between-group comparisons were performed by three-way repeated measures ANOVA with injection and operation as between-subject factor, whereas prepulse intensity (74 and 78 dB) was treated as repeated measures variable. Additionally, two-way ANOVA was performed with injection and operation as between-subject factor in each prepulse intensity. For comparisons of SAs, two-way ANOVA was performed with injection and operation as between-subject factor.

RESULTS

Verification of lesions and location of microinjection cannulae

Nissl-stained sections showed neural loss and neuroglial proliferation that were confined to the left EC in the majority of subjects, as reported previously (Kurachi et al., 2000; Sumiyoshi et al., 2004, 2005; Uehara et al., 2003, 2004). Neural atrophy was observed in a part of the dentate gyrus and hippocampus in some cases.

Figure 1A illustrates the range of cannula placements and confirms the mPFC as the target site for the lidocaine infusions. All cannula were placed in the prelimbic or infralimbic areas. Figures 1B and 1C show the location of microdialysis probes in the NAC and BLA, respectively. Probe placements were mostly identified in the shell of NAC.

Effect of EC lesions and mPFC inactivation on basal DA release

Baseline values of DA concentrations (mean ± SEM) in the 20-min dialysates (picogram/40 μl) were: sham 4.69 ± 0.61 (n = 21) and lesion 5.49 ± 0.73 (n = 21) in the NAC; sham 2.43 ± 0.37 (n = 22) and lesion 1.78 ± 0.30 (n = 23) in the BLA. There were no significant differences in DA levels between sham-operated rats and lesioned animals in both regions [$F(1,40) = 0.71$, $P = 0.41$, and $F(1,42) = 1.93$, $P = 0.17$, respectively].

First, we studied the effects of lidocaine infusion into the mPFC on the basal extracellular DA concentrations in the NAC and BLA. In the NAC, lidocaine did not affect basal DA levels in sham-operated rats and lesioned animals (Figs. 2A and 2B). In the BLA, however, three-way ANOVA revealed a significant main effect of injection [$F(1,17) = 8.04$, $P = 0.01$] and injection × time interaction [$F(9,153) = 2.38$, $P = 0.02$] (Figs. 2C and 2D). These results indicate that lidocaine infusion into the mPFC decreased extracellular DA levels in the BLA, but not NAC, irrespective of the lesion status.

Effect of EC lesions and mPFC inactivation on MAP-induced DA release

Next, we examined the effects of lidocaine infusion into the mPFC and EC lesions on MAP-induced DA release. ANOVA revealed a significant operation × time interaction effect [$F(9,162) = 3.24$, $P = 0.001$] and injection × operation × time interaction [$F(9,162) = 3.36$, $P = 0.001$] for the NAC. Subsequent analysis was conducted to examine operation × time interaction effects in CSF- and lidocaine-injected animals separately. CSF infusion did not affect the ability of EC lesions to enhance MAP-induced DA release in the NAC, while lidocaine augmented MAP-induced DA release in the EC lesioned rats, as indicated by a significant operation × time interaction effect [$F(10,80) = 8.90$, $P < 0.0001$] (Figs. 3A and 3B).

In the BLA, ANOVA revealed a significant operation × time interaction effect [$F(9,180) = 2.54$, $P = 0.009$] with a marginal injection × time interaction effect [$F(9,180) = 1.92$, $P = 0.051$], while injection ×

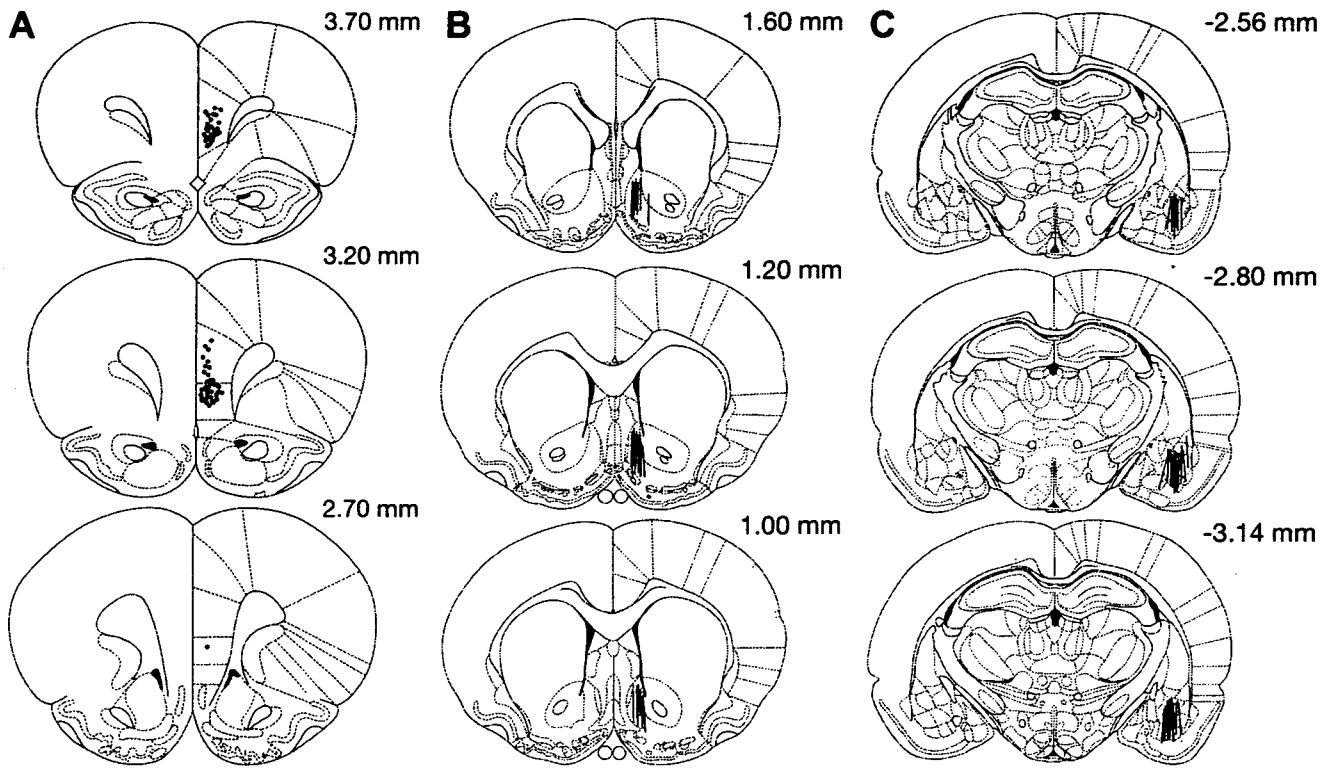

Fig. 1. Histological identification of the location of (**A**) cannula placements in the mPFC, (**B**) probes in the NAC, and (**C**) the BLA viewed in the coronal plane (sections taken from the atlas of Paxinos and Watson (1998)). The numbers refer to millimeter anterior to bregma.

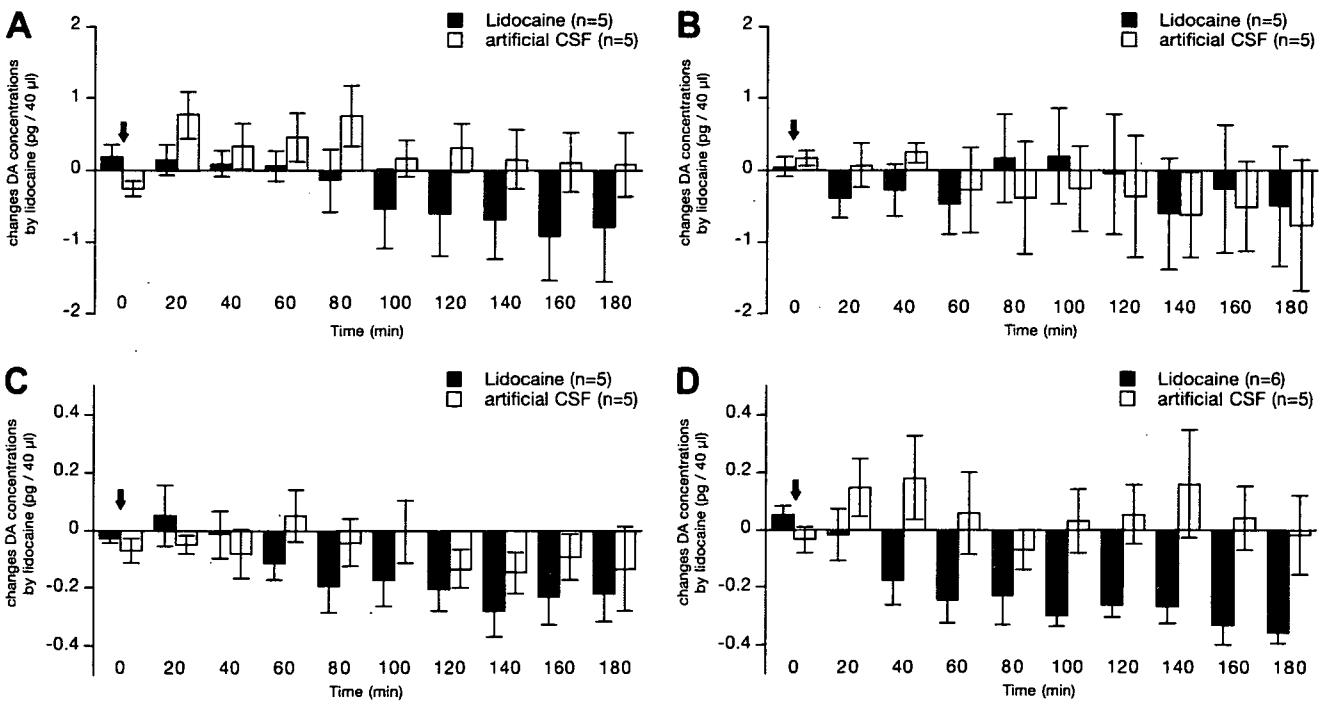

Fig. 2. Time course of the effect of lidocaine infusion into the mPFC on the extracellular DA concentrations in the NAC of sham-operated (**A**) and lesioned (**B**) rats, and in the BLA of sham-operated (**C**) and lesioned (**D**) rats. Arrows indicate the time of the infusion of lidocaine (shaded bars) and artificial CSF (open bars). Changes of DA concentrations in picogram/20 µl (20 min) samples calculated by subtracting the basal DA levels (the mean of three consecutive samples before lidocaine or artificial CSF administration) from DA concentrations at each time point. Values are expressed as mean ± SEM.

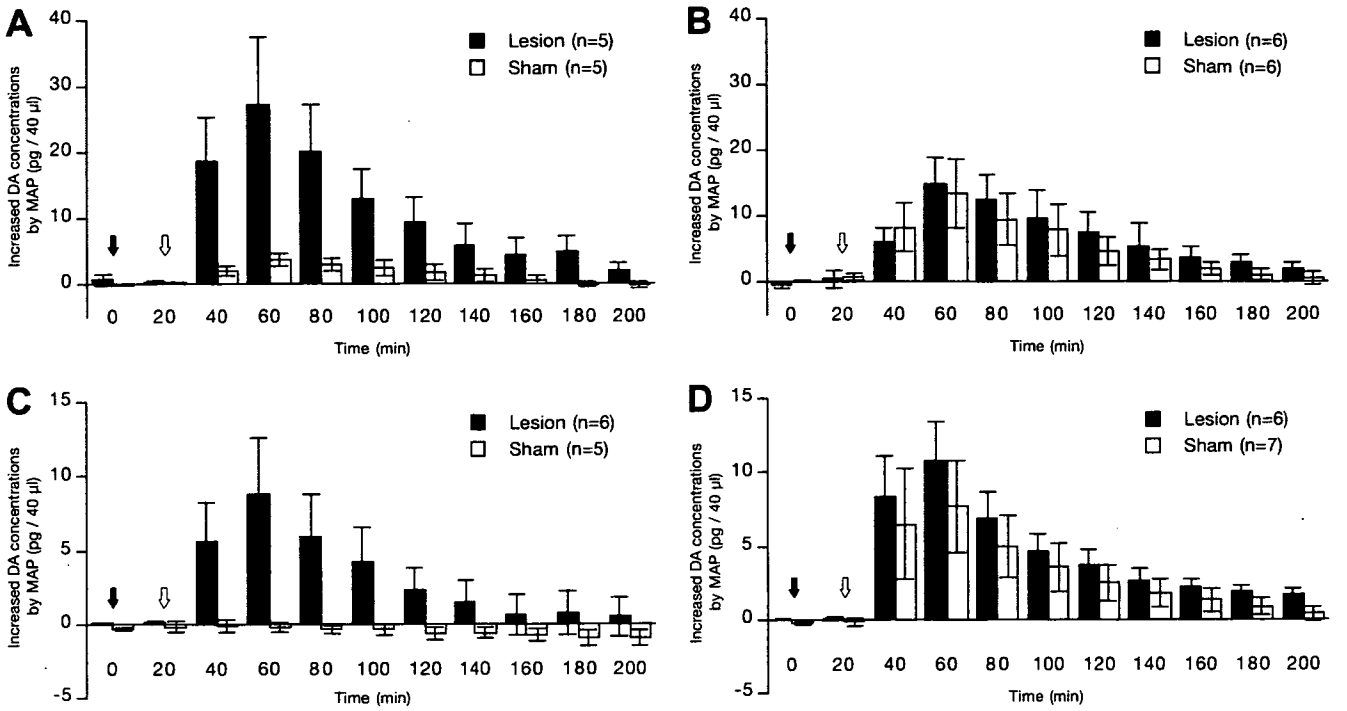

Fig. 3. Time course of the MAP (1.0 mg/kg, i.p.)-induced increase of extracellular DA concentrations in the NAC (**A** and **B**) and in the BLA (**C** and **D**) of sham-operated (open bars) and lesioned (shaded bars) rats. MAP was injected 20 min after lidocaine (A and C) or artificial CSF (B and D) infusion into the mPFC. Arrows indicate the point of drug administration (closed arrows, lidocaine; open arrows, MAP). MAP-induced increase in DA levels was calculated by subtracting the basal DA levels (the mean of three consecutive samples before lidocaine or artificial CSF administration) from MAP-induced DA release. Values are expressed as mean ± SEM.

operation × time interaction effect [$F(9,180) = 0.87$, $P = 0.56$] was not significant (Figs. 3C and 3D).

Effect of EC lesions and mPFC inactivation on MAP-induced locomotor activity

Figure 4 shows MAP-induced locomotor activity. Two-way ANOVA revealed a significant main effect of operation [$F(1.55) = 7.09$, $P = 0.01$] but not injection [$F(1.55) = 1.26$, $P = 0.27$], without a significant operation × injection interaction [$F(1.55) = 1.99$, $P = 0.16$]. The results indicate that EC lesions, but not inactivation of mPFC enhanced locomotion. Subsequent analysis was conducted to examine operation effects in CSF- and lidocaine-injected rats separately. Lidocaine infusion augmented the ability of EC lesions to enhance MAP-induced locomotor activity [$F(1,25) = 5.38$, $P = 0.029$], while CSF infusion did not [$F(1,30) = 1.32$, $P = 0.26$].

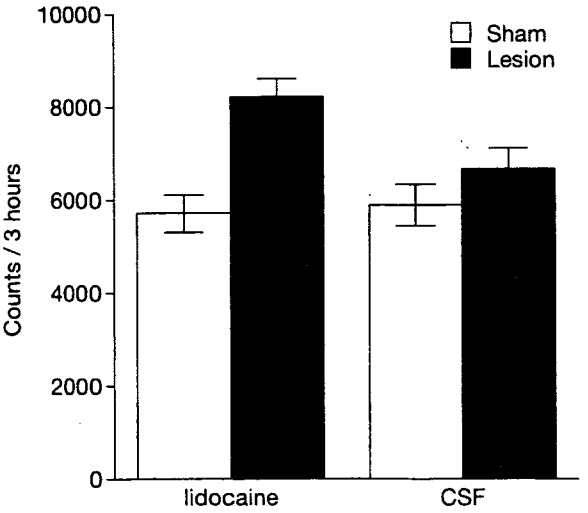

Fig. 4. Locomotor activity of EC lesioned rats (shaded bar; lidocaine infusion $n = 14$, artificial CSF infusion $n = 17$) or sham-operated rats (open bar; lidocaine infusion $n = 17$, artificial CSF infusion $n = 18$) during 3 h after methamphetamine (1.0 mg/kg, i.p.) administration. Lidocaine was infused into the mPFC 20 min before MAP administration. Values are expressed as mean ± SEM. Asterisks indicate a significant difference in comparisons between lesioned and sham-operated rats in each microinjection status (one-way ANOVA).

Effect of EC lesions and mPFC inactivation on PPI

Two-way ANOVA demonstrated no significant main effects of injection [$F(1.51) = 0.23$, $P = 0.63$] and operation [$F(1,55) = 1.02$, $P = 0.32$], as well as their interaction [$F(1,55) = 0.44$, $P = 0.51$] on SA (Fig. 5A).

For PPI, three-way ANOVA indicated a significant main effect of prepulse (74, 78 dB) [$F(1,51) = 8.71$, $P = 0.005$] and operation × prepulse interaction [$F(1,51) = 5.66$, $P = 0.021$]. Subsequent analysis revealed a significant effect of injection [$F(1,51) = 6.58$, $P = 0.013$]. These results indicated that inactivation of mPFC by

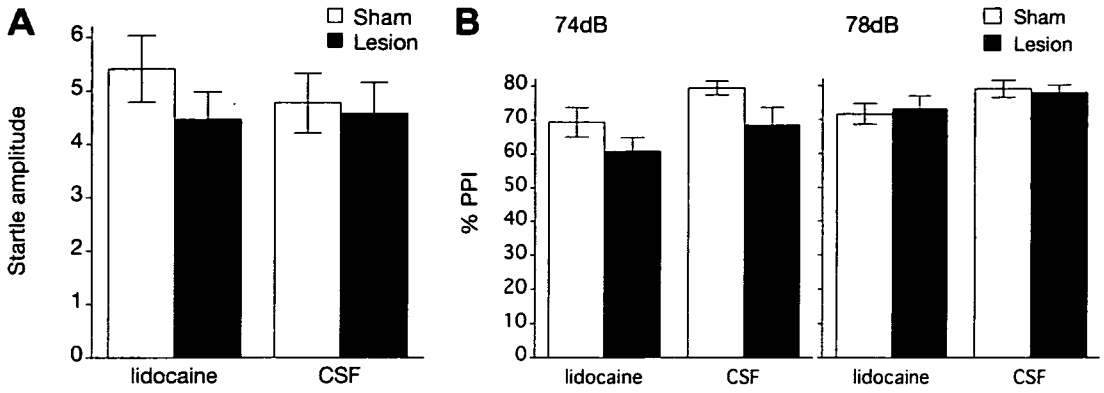

Fig. 5. **A:** Mean amplitudes of startle reflex on the single noise (120 dB) trials during PPI sessions. Data of EC lesioned rats (lidocaine infusion $n = 13$, artificial CSF infusion $n = 13$) are shown by shaded bars and sham-operated rats (lidocaine infusion $n = 17$, artificial CSF infusion $n = 18$) by open bars. Values are expressed as mean ± SEM. **B:** PPI with prepulses of 74 and 78 dB after lidocaine or artificial CSF infusion into the mPFC in EC lesioned rats (shaded bar; lidocaine infusion $n = 13$, artificial CSF infusion $n = 13$) and sham-operated rats (open bar; lidocaine infusion $n = 17$, artificial CSF infusion $n = 18$). Values are expressed as mean ± SEM.

TABLE I. Effects of mPFC inactivation and EC lesions on neurochemical and behavioral parameters

	NAC		BLA			
	Sham	EC-lesion	Sham	EC-lesion	EC- effect on LA	EC-lesion effect on PPI
Artificial CSF infusion					→	↓
Basal DA release	→	→	→	→		
MAP-induced DA release	(+)	(+)	(+)	⇑		
Lidocaine infusion					⇑	⇓
Basal DA release	→	→	↓	↓		
MAP-induced DA release	(+)	⇑	(−)	⇑		

→, no change compared with sham-operated rats; ↓, decrease compared with sham-operated rats; ⇑ and ⇓ significantly greater and lesser enhancement compared with sham-operated counterparts, respectively. mPFC, medial prefrontal cortex; NAC nucleus accumbens; BLA, basolateral amygdale; EC, entorhinal cortex; LA. Locomotor activity; PPI, prepulse inhibition; CSF, cerebrospinal fluid.

lidocaine infusion disrupted PPI, and that EC lesions reduced PPI in with the weaker prepulse (74 dB).

Table I shows the summary of the effects of EC lesions and mPFC inactivation on neurochemical and behavioral parameters.

DISCUSSION

This study was undertaken to determine if inactivation of the mPFC affects mesolimbic DA activity and PPI in rats with EC lesions. The results showed that infusion of lidocaine into the mPFC exhibits differential effects on DAergic neurotransmission in the NAC and BLA (Table I). Moreover, inactivation of the mPFC and EC lesions both disrupted sensorimotor gating, as demonstrated by reduced PPI.

Infusion of lidocaine causes neural inactivation by its local anesthetic effect via blockade of Na^+ channels (Catterall, 1980). The concentration and volume of lidocaine used in the current study was based on previous studies (Lomber, 1999; Tehovnik and Sommer, 1997; Woods and Ettenberg, 2004), which show neural inactivation that lasts 15–60 min (Lomber, 1999; Tehovnik and Sommer, 1997).

The current study demonstrated that lidocaine infusion into the mPFC reduced basal (tonic) DA release, and attenuated MAP (1.0 mg/kg, i.p.)-induced DA release in the BLA in both lesioned and sham-operated rats. The mPFC sends nerve projections to the BLA with glutamate as the transmitter (Brinley-Reed et al., 1995; McDonald, 1998; Sesack et al., 1989). It is possible that acute inactivation of the mPFC causes a decrease in these excitatory inputs, leading to reduced tonic and phasic (MAP-induced) DA release in the BLA. On the other hand, enhancement of MAP-induced DA release in the BLA of EC lesioned rats (Figs. 3C and 3D) is consistent with the results of our previous study (Uehara et al., 2004). Lesioning of EC for 4 weeks is thought to decrease extatory inputs into the BLA. These findings, suggestive of exaggerated phasic DA response, are in line with an increase in tissue concentrations of DA and new DA pool in nerve terminals in the BLA (Uehara et al., 2004), as well as enhancement of stress-induced DA release in the BLA (Uehara et al., 2003) of EC-lesion rats.

The major finding of this study is that inactivation of the mPFC augmented MAP (1.0 mg/kg, i.p.)-induced DA release in the NAC of EC-lesioned, but not sham-operated rats (Figs. 3A and 3B). The mPFC has been shown to regulate DA release in the NAC through its glutamatergic afferents to the ventral tegmental area (VTA) (Karreman and Moghaddam, 1996; Taber and Fibiger, 1995). Infusion of TTX into

the PFC causes a decrease in extracellular DA levels in the NAC (Karreman and Moghaddam, 1996). By contrast, a previous study (Murase et al., 1993) reports that microinfusion of lidocaine into the mPFC transiently reduces DA release in the NAC and burst firing in the VTA, suggesting that basal (tonic) DA release in the NAC is under a tonic excitatory control by the mPFC through glutamatergic projections to the DA cell body in the VTA. The discrepancy between the previous results and the present findings may be ascribed to the difference in the method of inactivation (i.e., TTX in the previous studies vs. lidocaine in this study) and/or other factors.

Stimulation of the BLA has been demonstrated to directly modulate the DA release in the NAC (Howland et al., 2002; Jackson and Moghaddam, 2001; Leonetti et al., 2006). Glutamate release from neurons originating from the BLA and projecting into the NAC has been shown to evoke local DA release in the NAC (Howland et al., 2002; Leonetti et al., 2006). Infusion of lidocaine into the BLA (Woods and Ettenberg, 2004), as well as DA-depleting (6-OHDA) lesions of the BLA (Simon et al., 1988), has been shown to enhance amphetamine-induced locomotor response without affecting spontaneous locomotion. Likewise, an in vivo voltametry study showed that 6-OHDA lesions of the BLA increased the DA signaling in the NAC in response to tail pinch or predor odor stress (Stevenson et al., 2003), although infusion of lidocaine into the mPFC was reported not to block the BLA stimulation-evoked increase in DA release in the NAC (Howland et al., 2002). These results overall suggest that decreasing tonic DA activity in the BLA may enhance phasic DA transmission without significant changes in tonic DAergic activity in the NAC, and that reduced MAP-induced DA release in the BLA may contribute to augmented DAergic activity in the NAC in rats with EC lesions during inactivation of the mPFC.

Left EC lesions significantly increased MAP-induced locomotor activity, replicating the results of our previous study (Sumiyoshi et al., 2004). In that study, the EC lesioned rats did not show a significant change in MAP (1 mg/kg, i.p.)-induced DA release in the NAC compared to sham-operated animals, while the EC lesioned rats exhibited significantly greater MAP-induced locomotor activity than did sham-operated animals (Sumiyoshi et al., 2004). A subsequent study (Sumiyoshi et al., 2005) reports a marked (twofold) increase in the proportion of the high-affinity state of D2 receptors in the striatum of EC lesioned rats without a change in the D1 receptor component. These results indicate supersensitivity of subcortical D2 receptors in rats with excitotoxic damage to the EC (Seeman et al., 2006; Sumiyoshi et al., 2004, 2005). Moreover, the fact that lidocaine-injected rats demonstrated that a greater locomotor activity in the EC lesion rats is consistent with neurochemical data in the current study.

Inactivation of mPFC by lidocaine infusion, as well as EC lesions, reduced PPI without affecting SAs. PPI has been shown to reflect the activation of limbic and cortico–pallido–striato–thalamic circuitry that mediates sensorimotor gating (Koch and Schnitzler, 1997; Swerdlow et al., 2001). DA projections to the NAC are considered to play an important role in mediating PPI (Swerdlow et al., 1990a,b; Zhang et al., 2000). PPI is also modulated by DA transmissions in the BLA, independent of changes in those in the NAC (Stevenson and Gratton, 2004). In the current study, PPI was disrupted by lidocaine infusion into the mPFC. Although basal DA release in the NAC was not changed during inactivation of mPFC (Figs. 2A and 2B), MAP-induced DA release was increased by mPFC inactivation in EC lesioned rats. On the other hand, lidocaine infusion into the mPFC decreased basal DA release in the BLA. Moreover, inactivation of mPFC attenuated MAP-induced DA release. These findings suggest that mPFC inactivation leads to dysfunction of tonic and phasic DAergic neurotransmission in the NAC and BLA, providing a possible mechanism by which mPFC inactivation disrupted PPI.

EC lesions produced disruption of PPI without affecting SAs, similar to the findings in rats with bilateral EC lesions (Goto et al., 2002). In the present study, EC lesions did not change basal DA release in the NAC. On the other hand, EC lesions have been demonstrated to produce an increase in the proportion of the high-affinity state of D2 receptors in the striatum of rats without a change in D1 receptor component (Sumiyoshi et al., 2005). Therefore, it is likely that PPI disruption in the lesion rats was mediated by postsynaptic DA supersensitivity in the NAC of EC lesioned rats (Sumiyoshi et al., 2004). Blockade of D1 and D2/D3 receptors in the BLA has been reported to produce opposite effects on PPI. Thus, PPI is disrupted by D2/D3 receptor antagonists, whereas it is enhanced by D1 receptor blockade (Stevenson and Gratton, 2004). As mentioned above, the lesioned animals do not show a change in the proportion of the high-affinity state of the D3 receptor subtype (Seeman et al., 2006). These results suggest a contribution of supersensitivity of postsynaptic D2 receptors in the BLA to the disruption of PPI in rats with EC lesions. Further studies are warranted to investigate the role for other DA receptor subtypes in impaired sensorimotor gating in animals with EC lesions.

In the present study, lidocaine was infused into the left mPFC in the behavioral experiments (locomotion, PPI) to produce the same condition as in the microdialysis experiments. Because prefrontal cortex connects with the bilateral BLA (Granato et al., 1991), inactivation of the left mPFC may have affected neural activity of not only the ipsilateral but also contra-

lateral BLA. It is worthwhile to investigate the long-term effect of continuous mPFC inactivation on the limbic DAergic neurotransmission and related behaviors in animals with EC lesions.

The volume reduction in the parahippocampal gyrus has been reported to be correlated with the severity of positive psychotic symptoms of schizophrenia (Bogerts, 1997). A morphological study from our laboratory suggests that the severity of Schneiderian symptoms is inversely correlated the left parahippocampal gyrus volumes (Suzuki et al., 2005a). On the other hand, greater PPI has been associated with higher relative metabolic activity rates in prefrontal cortex, as demonstrated by positron emission tomography (Hazlett et al., 1998). Moreover, better attentional modulation of PPI has been associated with higher frontal/occipital ratios of glucose metabolism in healthy subjects, but not patients with schizophrenia (Hazlett and Buchsbaum, 2001). These clinical observations may be relevant to the results presented here, showing that rats with excitotoxic lesions of the left EC and/or inactivation of mPFC elicit abnormal DAergic activity.

In conclusion, the results of this study indicate that inactivation of the mPFC, as well as EC lesions, leads to dysregulation of DAergic transmissions in the limbic regions. The findings that inactivation of the mPFC in rats with EC lesions augmented MAP-induced DA release in the NAC and disrupted PPI may support the hypothesis that dysfunction of prefrontal cortex may play a crucial role in the manifestation of psychosis in subjects with volume reductions in the medial temporal lobe structures (Kurachi, 2003a,b; Siever and Davis, 2004; Suzuki et al., 2005b). Investigations into the functional state of DA receptor subtypes in the EC lesion rats under mPFC inactivation are warranted to further examine the construct validity of these rats as an animal model of psychosis vulnerability (Seeman et al. 2006; Sumiyoshi et al. 2004, 2005).

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Prevalence of large cavum septi pellucidi and its relation to the medial temporal lobe structures in schizophrenia spectrum

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Abstract

Magnetic resonance imaging was used to evaluate the prevalence of the cavum septi pellucidi (CSP) in 154 schizophrenia patients, 47 schizotypal disorder patients, and 163 healthy controls. We also explored the relation of a large CSP (≥6 mm) with medial temporal lobe structures. No significant difference was found in the prevalence of the CSP (76.0% of the schizophrenia patients, 81.6% of the controls, and 85.1% of the schizotypal patients) or the large CSP (6.5% of the schizophrenia patients, 7.4% of the controls, and 10.6% of the schizotypal patients) among the groups, but patients with a large CSP (10 schizophrenia and 5 schizotypal patients) had smaller volumes of bilateral amygdala and left posterior parahippocampal gyrus than patients without it. In the control subjects, the large CSP did not affect the volumes of the medial temporal lobe structures. These findings might reflect neurodevelopmental abnormalities in midline and associated limbic structures of the brain in schizophrenia spectrum.

Keywords: Amygdala; Cavum septi pellucidi; Magnetic resonance imaging; Schizophrenia; Schizotypal disorder

1. Introduction

Septum pellucidi is a component of the limbic system and plays a crucial role in the connection between the hypothalamus and the hippocampus, amygdala, habenula, and brain-stem reticular formation (Sarwar, 1989). The cavum septi pellucidi (CSP), which is caused by an incomplete fusion of the septum pellucidi, is thought to be a normal anatomical variant, but unusually large CSP has been implicated in fetal neurodevelopmental abnormalities and its presence might reflect abnormalities in the development of the corpus callosum and limbic system structures including the amygdala and hippocampus (Bodensteiner and Schaefer, 1990; Rakic and Yakovlev, 1968; Sarwar, 1989; Shaw and Alvord, 1969).

Several magnetic resonance imaging (MRI) studies in schizophrenia have reported an increased prevalence of the large CSP (de Souza Crippa et al., 2006; Nopoulos et al., 1997, 1998) and its relation to the morphologic changes of the medial temporal lobe structures (Kasai et al., 2004; Kwon et al., 1998). These findings in schizophrenia may reflect the abnormal neurodevelopment in midline and associated limbic structures (Sarwar, 1989), while not consistently replicated (Flashman et al., 2007; Keshavan et al., 2002a,b; Rajarethinam et al.,

Abbreviations: ANOVA, Analysis of variance; CASH, Comprehensive Assessment of Symptoms and History; CSP, Cavum septi pellucidi; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; ICC, Intraclass correlation coefficient; ICD-10, International Classification of Diseases, 10th edition; ICV, Intracranial volume; MANCOVA, Multivariate analysis of covariance; MRI, Magnetic resonance imaging; SCID-II, Structured Clinical Interview for DSM-IV axis II disorders; SPD, Schizotypal personality disorder.

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2001). Also in our previous study using high-resolution MRI (Hagino et al., 2001), we failed to find a higher prevalence of the large CSP in schizophrenia patients despite a relatively large sample size (86 patients and 79 healthy comparisons). The difference in the prevalence of the large CSP between schizophrenia patients and healthy subjects, if present, is considered to be relatively small, and more cases of a large CSP would be required to elucidate the implications of this abnormality in schizophrenia.

Pathological deviations genetically and phenomenologically related to schizophrenia are grouped under the schizophrenia spectrum. This concept reflects the assumption that schizophrenia has a multifactorial aetiology in which multiple susceptibility genes interact with environmental insults to yield a range of phenotypes (Siever and Davis, 2004). Schizotypal (personality) disorder (SPD) is thought to be a prototypic disorder within the schizophrenia spectrum (Siever et al., 2002), characterized by odd behavior and attenuated forms of schizophrenic features without the manifestation of an overt and sustained psychosis (American Psychiatric Association, 1994; World Health Organization, 1992). It is genetically related to schizophrenia (Kendler et al., 1993; Siever et al., 1990) and might share neurodevelopmental abnormalities with schizophrenia as a common neurobiological basis for vulnerability factors as part of the schizophrenia spectrum. To our knowledge, however, only two MRI studies have evaluated the CSP in schizotypal subjects, where a trend toward an elevated rate of a large CSP was found in a relatively small sample of SPD subjects (Dickey et al., 2007; Kwon et al., 1998).

In this study, we used MRI to evaluate the prevalence of the CSP in an extended sample of normal controls and schizophrenia patients as well as in schizotypal disorder patients. We also investigated the relation between the large CSP and medial temporal lobe structures in a sub-sample of schizophrenia spectrum disorders and healthy controls. On the basis of our previous study (Hagino et al., 2001) and hypothesized abnormal neurodevelopment in midline and medial temporal lobe structures in schizophrenia (Kasai et al., 2004; Kwon et al., 1998), we predicted that the prevalence of the large CSP would not differ among the groups, but that it would affect the medial temporal morphology.

2. Methods

2.1. Subjects

Demographic and clinical data of the subjects in this study are presented in Table 1. This cohort includes 86 schizophrenia patients and 79 healthy controls investigated in our former CSP study (Hagino et al., 2001). All subjects were right-handed and physically healthy at the time of the study, and none had a lifetime history of serious head trauma, neurological illness, serious medical or surgical illness, or substance abuse. The three groups were matched for age, gender, and height.

One hundred fifty-four schizophrenia patients (79 inpatients and 75 outpatients) who met the ICD-10 criteria for research (World Health Organization, 1993) were recruited from the inpatient and outpatient clinics of the Department of Neuropsychiatry, Toyama University Hospital. Diagnoses were made following structured clinical interviews by psychiatrists with the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al., 1992). One hundred forty-eight patients were receiving neuroleptic medication; 90 were being treated with typical neuroleptics and 58 were receiving atypical neuroleptics. Clinical symptoms were rated by well-trained psychiatrists at the time of scanning using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984) and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984).

Forty-seven schizotypal disorder patients were recruited from among the patients who visited the clinics with schizotypal features accompanied by distress or associated problems in their lives. The sample characteristics of the clinic-based schizotypal subjects in our laboratory have been described in detail elsewhere (Takahashi et al., 2006). Structured clinical interviews were performed using the CASH (Andreasen et al., 1992) and Structured Clinical Interview for DSM-IV axis II disorders

Table 1
Clinical and demographic characteristics of patients with schizophrenia, patients with schizotypal disorder, and normal control subjects[a]

	Schizophrenia patients	Schizotypal patients	Control subjects
	$N=154$	$N=47$	$N=163$
	($N=69$)	($N=36$)	($N=72$)
Male/female	74/80	29/18	97/66
	(35/34)	(24/12)	(43/29)
Age (years)	28.0 ±7.8	25.0±5.4	27.0±8.0
	(26.3±5.7)	(25.8±5.4)	(24.9±5.9)
Height (cm)	163.8±7.6	165.9±8.7	165.7±8.2
	(164.6±7.7)	(165.9±9.0)	(166.9±7.3)
Education (years)	13.0±2.0	13.1±2.0	15.9[b]±2.7
	(13.5±1.9)	(13.6±1.8)	(16.2[b]±2.6)
Parental education (years)	12.2±2.3	12.3±1.7	13.1[c]±2.6
	(12.0±2.1)	(12.2±1.8)	(13.0[c]±2.5)
Age at onset (years)	23.0±6.4	–	–
	(21.8±4.3)	(–)	(–)
Duration of illness (years)	5.1±5.5	–	–
	(4.6±5.1)	(–)	(–)
Duration of medication (years)	3.6[d]±4.7	1.5±3.0	–
	(3.5[d]±4.3)	(1.8±3.3)	(–)
Drug (mg/day, haloperidol equiv.)	10.3[d]±8.4	4.8±5.7	–
	(11.6[d]±9.3)	(4.2 ± 4.7)	(–)
Total SAPS score	26.9[d]±21.8	15.9±9.3	–
	(25.9[d]±20.4)	(16.6±9.0)	(–)
Total SANS score	49.6[e]±21.2	41.9±22.6	–
	(46.7±23.1)	(42.6±22.9)	(–)

The values represent means±SDs. SANS, Scale for the Assessment of Negative Symptoms (Andreasen, 1984); SAPS, Scale for the Assessment of Positive Symptoms (Andreasen, 1984).
ANOVA followed by Scheffé's test was used.
[a] The values in parentheses show the data of the sub-sample for whom volumetric data were available.
[b] $p<0.01$: compared to the schizophrenia and schizotypal patients.
[c] $p<0.05$: compared to the schizophrenia patients.
[d] $p<0.01$: compared to the schizotypal patients.
[e] $p<0.05$: compared to the schizotypal patients.

(SCID-II) (First et al., 1997). They all met the criteria for schizotypal disorder in the ICD-10 (World Health Organization, 1993) as well as the criteria for schizotypal personality disorder in the DSM-IV (American Psychiatric Association, 1994). Based on the data from the CASH and SCID-II, subjects were diagnosed by the consensus of at least two experienced psychiatrists. All subjects have received consistent clinical follow-up. One male subject has developed schizophrenia after scanning, but none of the other schizotypal subjects has developed overt psychosis to date (mean follow-up period after MRI scanning=2.9 years, SD=2.5). Thirty-four patients were outpatients, and the other 13 underwent closer clinical and medical examinations including MRI during short-term admission. At the time of MRI scanning, 40 of the 47 patients were treated with low-dose antipsychotics, of which 14 were treated with typical neuroleptics and 26 received atypical neuroleptics. The remaining six patients were neuroleptic-naïve. Clinical symptoms were rated at the time of scanning using the SANS and SAPS.

The controls subjects consisted of 163 healthy volunteers recruited from among members of the community, hospital staff, and university students. They were given a questionnaire consisting of 15 items concerning their family and past histories, as well as present illness. They did not have any personal or family history of psychiatric illness in their first-degree relatives. The control subjects were not screened with a standard measure such as a SCID-II and this may be a possible limitation of the study. However, all control candidates were interviewed and administered the Minnesota Multiphasic Personality Inventory (MMPI) by experienced clinical psychologists in order to obtain a rather homogeneous control group without eccentric profiles on the MMPI. Although the MMPI has not proved very sensitive for the detection of schizotypy (Walters, 1983), approximately 17% of the candidates for normal controls were excluded for having an abnormal profile with a *T*-score for the validity scales or the clinical scales exceeding 70.

Volumetric measurements of the medial temporal lobe structures were available for 69 schizophrenia patients, 36 schizotypal patients, and 72 controls (Table 1). This subgroup included 137 subjects from our previous study (Suzuki et al., 2005), which investigated the medial temporal and frontal lobe structures in the schizophrenia spectrum, and an additional 40 subjects; all the subjects with a large CSP in our entire sample (10 schizophrenia patients, 5 schizotypal patients, and 12 controls) were enrolled in the volumetric analysis in order to explore the relation of a large CSP with medial temporal lobe structures. The characteristics of this sub-sample seem to be largely comparable with those of the whole sample of the present study (Table 1). However, this cohort was somewhat younger than the whole sample, since we included relatively young schizophrenia patients and age-matched controls for the volumetric analyses in order to reduce the confounds in the data due to the medication and chronicity of illness. This study was approved by the Committee on Medical Ethics of University of Toyama. After a complete description of the study, written informed consent was obtained from all subjects.

2.2. MRI data acquisition and image analysis

MRI scans were acquired with a 1.5-T scanner (Vision; Siemens Medical System, Erlangen, Germany). A three-dimensional T1-weighted gradient-echo sequence FLASH (fast low-angle shots) with 1×1×1 mm voxels was used. Imaging parameters were: TE=5 ms; TR=24 ms; flip angle=40°, field of view=256 mm; matrix size=256×256. The image data were transferred to a Unix workstation (Silicon Graphics, Inc., Mountain View, CA, USA) and processed using the software package Dr View 5.3 (AJS, Tokyo, Japan). Brain images were realigned in three dimensions and reconstructed into entire contiguous coronal images, with a 1-mm thickness, perpendicular to the intercommissural line. The intracranial volume (ICV) was measured to correct for differences in head size as previously described (Zhou et al., 2003); the three groups for whom volumetric data were available did not significantly differ in their ICV volumes [repeated measures multivariate analysis of covariance (MANCOVA) with age and height as covariates, $F=1.39$, $df=2, 172$, $p=0.251$].

For the assessment of the CSP, the number of coronal slices where a cavum was seen was counted (Hagino et al., 2001; Nopoulos et al., 1997, 1998). Since the images were 1-mm thick without gap, the rating was a reflection of the actual anterior-to-posterior length of the cavum. A CSP equal to or greater than 6 mm in length was defined as large. All images were assessed by one rater (TT) without any knowledge of the subjects' identity, gender, or diagnosis. Inter-(TT and HH) and intra-rater intraclass correlation coefficients (ICC) in 30 randomly selected brains were over 0.97 for ratings of the CSP.

The amygdala, hippocampus, and parahippocampal gyrus were manually traced on 1-mm consecutive coronal slices with the corresponding sagittal and axial planes simultaneously presented for reference. The procedures for delineation of these structures were described in detail previously (Niu et al., 2004; Suzuki et al., 2005). The inferior border of the amygdala in contact with the hippocampus head was determined by reference to the sagittal plane; the alveus was used to differentiate these structures. The parahippocampal gyrus was subdivided into anterior and posterior parts at the level of the posterior edge of the mammillary body. Three trained raters (TT, HH, and LN), who were blinded to the subjects' identity, gender, diagnosis, and information about the CSP (length, large or non-large), measured the volumes of these structures. Inter- and intra-rater ICCs in five randomly selected brains were over 0.90.

2.3. Statistical analysis

Chi-square tests, or Fisher's exact tests when expected cell sizes were less than five, were used for assessing the frequency of the CSP. To explore the relation of a large CSP (≥6 mm) with medial temporal lobe structures in a sub-sample for whom volumetric data were available, relative volumes (100×absolute volume/ICV) were analyzed using a repeated measures multivariate analysis of covariance (MANCOVA) for each ROI, with age, duration of neuroleptic medication, and medication dosage as covariates, diagnosis [schizophrenia spectrum patients

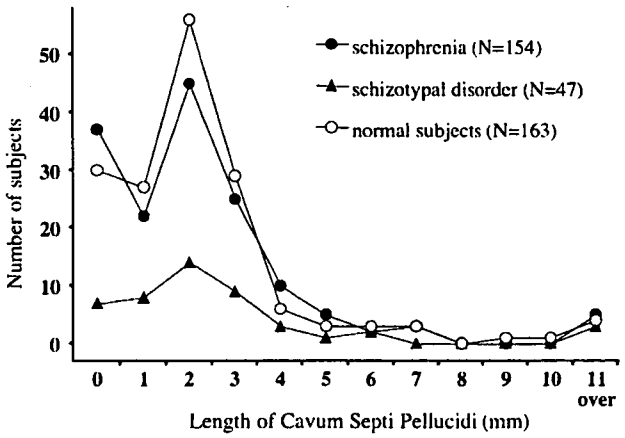

Fig. 1. Length of the cavum septi pellucidi (CSP) in patients with schizophrenia, patients with schizotypal disorder, and normal control subjects. No difference was found in the prevalence of the CSP among the three groups.

(schizophrenia and schizotypal disorder patients) versus controls] and CSP (large versus non-large CSP) as between-subject factors, and hemisphere as a within-subject variable. Since patients with schizophrenia are the main clinical group of interest, the relation between the large CSP and medial temporal lobe structures was also analyzed for only schizophrenia patients and controls. The volumetric measures for all ROIs in this study were normally distributed (tested by Kolmogorov–Smirnov test). The post hoc Scheffé's test was employed.

For patients with schizophrenia spectrum disorders, the relationships between the length of the CSP and relative volumes of the medial temporal lobe structures were examined by Pearson's partial correlation coefficients controlling for potential confounders such as age, duration of neuroleptic medication, and medication dosage. For these analyses, the subjects without CSP (12 schizophrenia and 4 schizotypal patients) were regarded as having a CSP of 0.5 mm and then the length of the CSP was log-transformed because of their skewed distribution. Statistical significance was defined as $P<0.05$ (two-tailed).

3. Results

The prevalence of the CSP was 76.0% (117/154) in the schizophrenia patients, 81.6% (133/163) in the controls, and 85.1% (40/47) in the schizotypal patients (Fig. 1), showing no group differences (chi-square=2.53, $p=0.28$). No difference was found in the prevalence of the large CSP among the diagnostic groups [6.5% (10/154) of the schizophrenia patients, 7.4% (12/163) of the controls, and 10.6% (5/47) of the schizotypal patients] ($p=0.64$, Fisher's exact probability test). There was no significant gender difference in the prevalence of the CSP or a large CSP in any of the diagnostic groups.

For the relationship between the large CSP and the medial temporal lobe structures (Table 2), MANCOVA of amygdala volume revealed a significant diagnosis-by-CSP interaction, with the subjects who had a large CSP having bilaterally smaller amygdala volumes than the subjects without a large CSP for the schizophrenia spectrum patients (Scheffé's test, $p<0.001$) but not for the control subjects (Scheffé's test, $p=0.996$). A significant diagnosis-by-CSP-by-hemisphere interaction for the volume of the posterior parahippocampal gyrus was also demonstrated ($F=8.07$, $df=1$, 173, $p=0.005$); the patients with schizophrenia spectrum disorders with a large CSP had a smaller left posterior parahippocampal gyrus than did the patients without a large CSP (Scheffé's test, $p<0.001$), while there was no difference in the volume of the left posterior parahippocampal gyrus between controls with and without a large CSP (Scheffé's test, $p=1.000$). When only the schizophrenia patients and controls were included in the analyses, we also found a significant diagnosis-by-CSP interaction for the relative volume of the amygdala ($F=7.41$, $df=1$, 134,

Table 2
Absolute volume for regions of interest in subjects with or without a large cavum septi pellucidi (CSP)[a]

	Healthy controls		Schizophrenia spectrum patients		Analysis of covariance ($df=1$, 170)[b]					
	Non-large CSP	Large CSP	Non-large CSP	Large CSP	Effect of CSP		Effect of diagnosis		Diagnosis × CSP	
Brain region (cm^3)	($N=60$)	($N=12$)	($N=90$)	($N=15$)	F	P	F	P	F	P
Amygdala					7.45	0.007	32.15	<0.001	5.85	0.017
Left	1.12±0.14	1.18±0.12	0.99±0.15	0.84±0.11						
Right	1.15±0.14	1.15±0.10	1.02±0.16	0.94±0.16						
Hippocampus					0.38	0.537	2.88	0.091	0.13	0.715
Left	3.01±0.41	3.14±0.41	2.84±0.39	2.93±0.42						
Right	3.21±0.36	3.28±0.65	3.07±0.43	3.00±0.44						
Anterior PHG					1.53	0.218	0.00	0.973	0.04	0.844
Left	2.40±0.59	2.73±0.62	2.48±0.47	2.81±0.43						
Right	2.78±0.58	2.94±0.46	2.76±0.55	2.87±0.55						
Posterior PHG					4.83	0.029	2.16	0.143	0.63	0.430
Left	4.71±0.56	4.78±0.84	4.67±0.67	4.25±0.60						
Right	4.50±0.45	4.44±0.61	4.39±0.55	4.45±0.53						

CSP, cavum septi pellucidi; PHG, parahippocampal gyrus.
Values represent means±SDs.
[a] The absolute volumes are shown in the table, but the statistical analyses reported here are based on the relative volumes (100 × absolute volume / intracranial volume).
[b] Diagnosis-by-CSP-by-hemisphere interaction was observed only for the posterior parahippocampal gyrus.

$p=0.007$) and a significant diagnosis-by-CSP-by-hemisphere interaction for the relative volume of the posterior parahippocampal gyrus ($F=8.10$, $df=1$, 137, $p=0.005$). The post hoc Scheffé's tests showed that the schizophrenia patients with a large CSP had smaller volumes of bilateral amygdala ($p<0.001$) and left posterior parahippocampal gyrus ($p=0.012$) than the patients without it. The effect involving the CSP was not significant for the other regions measured in this study.

Based on the results of the above-mentioned MANCOVA analyses, the correlational analyses between the length of the CSP and ROI volumes were adopted only for the bilateral amygdala and left posterior parahippocampal gyrus in schizophrenia spectrum patients in order to prevent possible type I error. The length of the CSP (log) was negatively correlated with the relative volumes of the amygdala (left, $r=-0.319$, $p=0.001$; right, $r=-0.222$, $p=0.025$) and left posterior parahippocampal gyrus ($r=-0.356$, $p<0.001$).

4. Discussion

In this study, no difference was found in the prevalence of the CSP or a large CSP between the large sample of schizophrenia patients, schizotypal disorder patients, and healthy controls. However, the volumes for bilateral amygdala and the left posterior parahippocampal gyrus in patients with schizophrenia spectrum disorders (schizophrenia and schizotypal disorder combined) were significantly smaller in those who had a large CSP than in those who did not.

The present finding of a high prevalence of the CSP, which is caused by an incomplete fusion of the septum pellucidi during fetal development, in all diagnostic groups supports the notion that the CSP itself is a normal anatomical variant (Nopoulos et al., 1997; Sarwar, 1989). On the other hand, an abnormally large CSP has been implicated in a midline neurodevelopmental anomaly involving a limbic system structure though definition of the large CSP as well as its clinical importance has not been established (Sarwar, 1989). We did not find an increased prevalence in schizophrenia or schizotypal patients compared with control subjects, while several (de Souza Crippa et al., 2006; Kasai et al., 2004; Kwon et al., 1998; Nopoulos et al., 1997) but not all (Flashman et al., 2007; Keshavan et al., 2002a,b; Rajarethinam et al., 2001) studies using high-resolution MRI have reported an increased prevalence of a large CSP in schizophrenia. The reason for these discrepancies is unclear because most studies used basically the same definition for a large CSP (≥ 6 mm), but the current study could be strengthened by the larger sample size compared with those in previous studies that reported an increased prevalence of a large CSP in schizophrenia (29 to 38 patients). The wide variance in the prevalence of a large CSP in schizophrenia reported to date (approximately from 4 to 30%) could be partly explained by differences in imaging techniques or sample characteristics (e.g., race, gender) among the reports. For schizotypal personality disorder patients, previous data indicated that a large CSP is relatively common [5/20 (25%) female (Dickey et al., 2007) and 3/16 (18.8%) male (Kwon et al., 1998) patients]. Although we failed to replicate these findings, abnormalities in midline structures in the schizophrenia spectrum seem worthy of further examination in a larger sample.

Regarding the relation of a large CSP with medial temporal lobe morphology in the schizophrenia spectrum, the patients with a large CSP had a significantly smaller bilateral amygdala than the patients without it. The left posterior parahippocampal gyrus was also smaller in the patients with a large CSP. These findings are consistent with previous MRI studies showing a similar association between a large CSP and volume of the left parahippocampal gyrus (Kasai et al., 2004) or bilateral amygdala–hippocampal complex (Kwon et al., 1998) in schizophrenia. In normal development, the CSP is consistently present in prematures but begins to close just before term and its prevalence is 15% at 3–6 months of birth (Sarwar, 1989; Shaw and Alvord, 1969). Although it is not clear what causes the obliteration of the CSP in most individuals several months after birth, Sarwar (1989) hypothesized that fusion of the septum pellucidi might be caused by rapid growth of the corpus callosum and the limbic system structures such as the hippocampus and amygdala. A reduction in the volume of the medial temporal lobe is suggested to have already occurred at the onset

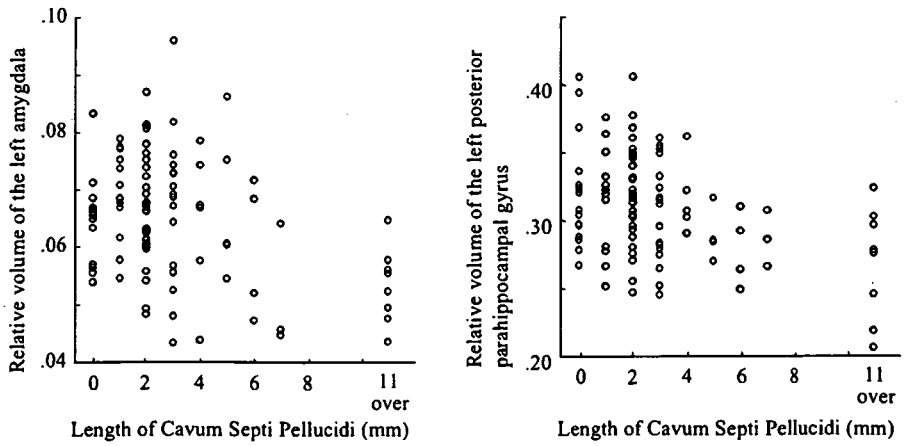

Fig. 2. Scatter plots for the length of the cavum septi pellucidi and relative volumes of the left amygdala and left posterior parahippocampal gyrus in patients with schizophrenia spectrum disorders.

of schizophrenia (Shenton et al., 2001) and has been identified also in subjects at genetic high-risk of developing schizophrenia (Keshavan et al., 2002a,b; Lawrie et al., 2001; Seidman et al., 2002) or in schizotypal subjects (Dickey et al., 2007; Suzuki et al., 2005). These findings are consistent with the neurodevelopmental model of schizophrenia (Weinberger, 1987) and suggest that abnormalities in the medial temporal lobe structures might indicate genetic vulnerability to schizophrenia. The distribution of the length of the CSP and its relation to the medial temporal morphology in this study (Fig. 2) might suggest that there is no obvious threshold effect between large (≥ 6 mm) and non-large (<6 mm) CSP on the volume of the medial temporal lobe structures in schizophrenia spectrum, and explicitly how neurodevelopmental abnormalities in the medial temporal lobe structures affect the process of the obliteration of the CSP in schizophrenia is obscure. Nevertheless, the present findings support a possible relationship between the neurodevelopment of the septum pellucidi and other limbic structures, and suggest that the presence of a large CSP could be a marker of the neurodevelopmental abnormalities in midline structures as well as related limbic structures, especially the amygdala, which may play an important role in the pathogenesis of schizophrenia (Kurachi, 2003).

A few possible confounding factors in this study need to be addressed. First, we did not separately investigate the relation of an abnormal CSP with the medial temporal lobe structures for schizophrenia and schizotypal disorder because of the small number of patients with a large CSP. Although the results were essentially the same even when we included only the schizophrenia patients and controls in the analyses, the neurobiological similarities and differences in the midline and associated limbic structures between established schizophrenia and a milder form of schizophrenia spectrum disorders remain to be further elucidated. Second, most patients in this study were on neuroleptic medication, which might affect the brain morphology. However, the dosage or duration of neuroleptic medication was not correlated with any of the volumetric measurements of the medial temporal lobe structures or the length of the CSP in either schizophrenia or schizotypal disorder patients.

5. Conclusion

We did not find an increased prevalence of the CSP or a large CSP in schizophrenia or schizotypal patients as compared with control subjects. However, the patients with a large CSP had significantly smaller volumes for bilateral amygdala and left posterior parahippocampal gyrus than the patients without it, possibly reflecting the neurodevelopmental abnormalities in midline and associated limbic structures of the brain in the schizophrenia spectrum.

Acknowledgements

This study was supported in part by Grant-in-Aid for Young Scientists 16790678 from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and a Research Grant (17-2, 18-6) for Nervous and Mental Disorders from the Ministry of Health, Labour and Welfare, Japan. The authors are grateful to Prof. Hideki Origasa, PhD, for helpful suggestions on statistical analyses.

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鹿児島県における司法精神鑑定の現状と課題

―医療観察法運用上の問題提起も含めて―

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堀切靖[2)]　小玉哲史[1)]　室屋真二[1)]　中村雅之[1)]
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心神喪失等の状態で重大な他害行為を行った者の医療及び観察等に関する法律（医療観察法）は，本邦初の司法精神医療に関する法律であるため，その現実的な運用面において様々な問題が発生することが予想される。特に，司法精神医学の観点からは，刑事訴訟法上の精神鑑定業務に加えて本法の業務が加わることにより，一部の精神科医の負担が増加することが予見される。そこで，我々は，司法精神鑑定を担当した経験のある一部の精神科医を対象に，鹿児島県（以下，本県）における精神鑑定の実状に関する予備的調査を行った。さらに，我々が経験した医療観察法対象者の処遇上の問題点を検討した。その結果，本県においては，司法精神医学教育の充実と，対象者の身体合併症に対応するための施設間連携の確立が急務であることが示唆された。今後，本法を円滑に運用していくためには，対象者の診断や処遇などの問題点を個々に検討していく必要があると考える。

九神精医　52：115-125，2006

Key words：forensic psychiatry, psychiatric evidence, serious crimes, mentally disordered offenders, criminal proceedings

はじめに

「心神喪失等の状態で重大な他害行為を行った者の医療及び観察等に関する法律」（以下，医療観察法）が，平成17年７月15日に施行された。医療観察法の目的は，第１条に規定されているように，心神喪失等の状態で重大な他害行為を行った者（以下，対象者）の精神障害を改善し，これに伴って同様の行為を行うことなく，社会復帰を促進することにある。しかし，本法は，わが国初ともいえる司法精神医療に係わる法律であるため，運用面における詳細な検討が不十分との指摘[7)]もあり，その運用面において様々な問題[7)8)11)13)]が発生することが予想される。

ところで，本県においては，指定通院医療機関が数カ所存在するのみで，指定入院医療機関は未だ整備されていないのが現状である。これは，本法が社会復帰を主たる目的としている観点からは，入院処遇を必要とする対象者が発生した場合，入院治療を本県以外の指定入院医療機関に依頼することにならざるを得ないため，本県では既に運用上の問題が発生していると言ってもよいであろう。この指定入院医療機関の問題に関しては，設備・人員配置など様々な障壁があることを指摘するにとどめ，詳細については本稿では割愛するが，指

〒890-8520 鹿児島県鹿児島市桜ヶ丘8-35-1

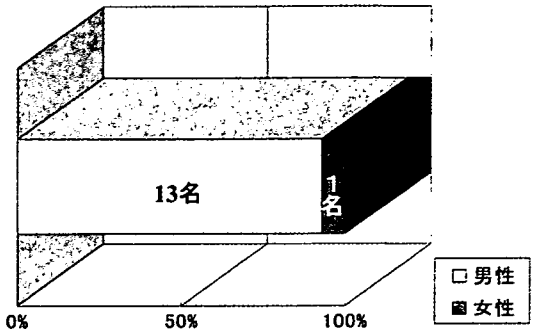

図 1　アンケートに回答した医師の性別

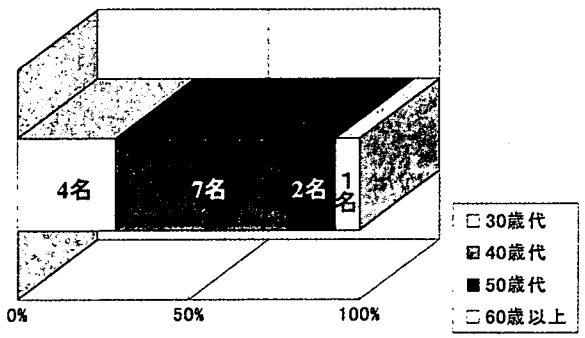

図 2　アンケートに回答した医師の年齢

定入院機関の充実に関しては，法律が施行された現在，本県のみならず，わが国全体でも早急に対応しなければならない問題である。

さて，医療観察法が施行されるに際し，本県における司法精神医療の状況で果たして本法を円滑に運用することができるのかということが懸念された。というのは，本県では，刑事訴訟法上の司法精神鑑定を一部の限られた精神科医が担当しているため，医療観察法の業務に携わるに足る精神保健審判員および鑑定人を確保することが困難なのではないかと思われたからである。幸い，精神保健審判員および鑑定人は確保されたようであるが，今後，司法精神医療に係わる精神科医の責務と負担が増加していくことが予想される。そこで，今回，我々は，一部の精神科医を対象にアンケートを実施し，まず，本県における精神鑑定の現状を調査した。その上で，我々が経験した医療観察法の対象事例を提示し，運用上の問題点および司法精神医学教育も含めた精神科医としての課題について報告する。

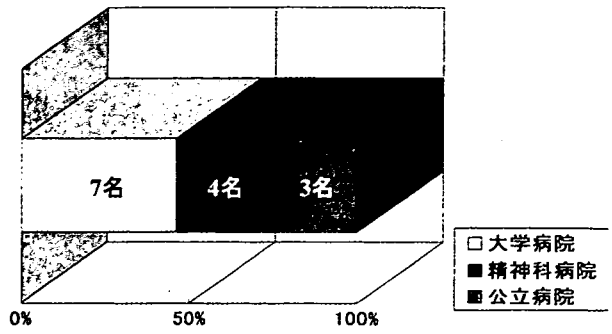

図 3　アンケートに回答した医師の勤務先

なお，今回，実施したアンケート調査は，一部の精神科医を対象とした予備的調査であり，本県において精神鑑定業務を担当した医師全てを網羅しているわけではないことを付記しておきたい。また，事例の記述に際しては，本人が特定されぬような配慮をし，論旨に支障のない範囲で病歴を改変したことも合わせて付記する。

調　査　方　法

アンケート用紙は，14名の精神科医に送付した。対象となった精神科医は，我々が所属している機関および関連施設に勤務し，かつ，過去に精神鑑定業務を担当した経験のある者に限定した。なお，アンケート用紙は無記名とし，鑑定内容に関する質問項目に関しては，被鑑定人が特定されることがないような倫理面への配慮を行った。

調　査　結　果

アンケートに回答した医師は14名（男性：13名，女性：1名）であった（図1）。年齢層は，30歳代が4名，40歳代が7名，50歳代が2名，60歳代が1名であった（図2）。

勤務先別では，大学病院に所属している医師が7名，精神科病院に所属している医師が4名，公立病院に所属している医師が3名であった(図3)。

精神鑑定業務を行った医師の精神科臨床経験年数は図4に示したが，10年未満の者はいなかった。また，全員が精神保健指定医であり，精神保健指定医取得後の精神科臨床経験年数は図5のとおりである。

図6には，精神鑑定業務の件数を示した。今回

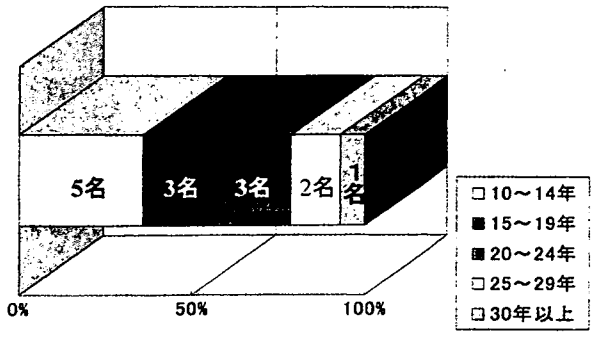

図 4　アンケートに回答した医師の精神科臨床経験年数

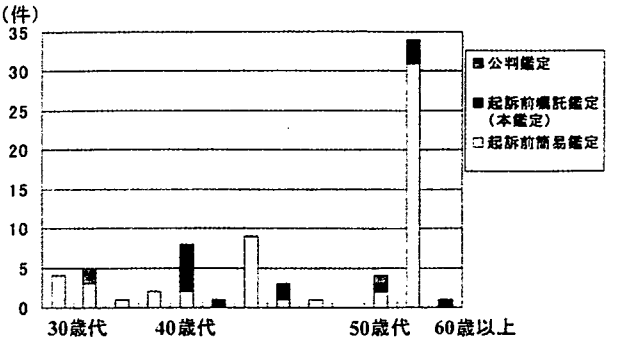

図 6　アンケートに回答した医師の過去５年間に担当した司法精神鑑定の件数

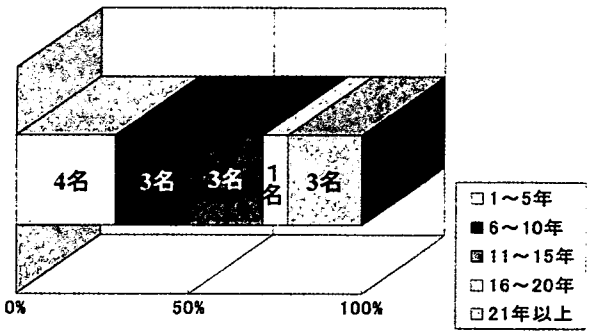

図 5　アンケートに回答した医師の精神保健指定医資格取得後の年数

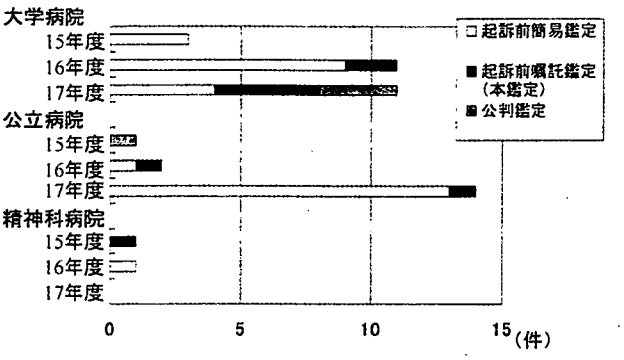

図 7　年代別・所属機関別にみた鑑定件数

は，アンケート調査時点で担当している精神鑑定も網羅できるように，調査期間を平成17年度を含む過去５年間とした。２名の医師は，対象期間以前に精神鑑定を担当していたため，図６に示した項目に関しては除外した。本県では，一部の限られた精神科医が精神鑑定業務を担当していることになるが，図６に示したように，その一部の精神科医の中でも担当した件数が，１件から30数件とばらつきがあった。担当した精神鑑定の内容に関しても簡易精神鑑定（簡易鑑定）のみ担当している医師，嘱託精神鑑定（本鑑定）の割合が簡易鑑定に比べ多い医師と様々であった。

図７には明確な回答が得られた３年間に限定し，精神鑑定の件数および内容を所属機関別に示した。これによると，大学病院が28件（本鑑定６件，簡易鑑定19件，公判鑑定３件），公立病院が17件（本鑑定２件，簡易鑑定14件，公判鑑定１件），精神科病院が２件（本鑑定１件，簡易鑑定１件）であった。

精神鑑定業務を初めて担当した際の精神科経験年数と，その時の鑑定の種類については，本鑑定を10年以下で担当した者が１名，10～15年で担当した者が２名であった。また，簡易鑑定が10年以下で３名，10～15年で４名，15～20年で１名であった。初めて担当した精神鑑定としては簡易鑑定が多かった（図８）。

昨年施行された医療観察法における精神鑑定については，調査した時点で１名の医師が担当していた。ただし，これは本県における医療観察法の適用状況全てを調査した結果ではないことを断っておく。

次に，今後，増加が予想される精神鑑定業務が実際に増えた場合，現状のままで対応できるのか否かを予測する意味で行った質問についてであるが，年間に引き受けることが可能な精神鑑定の種類と，その件数について図９のような回答が得られた。

最後に，自由な意見を求める形式の質問として，

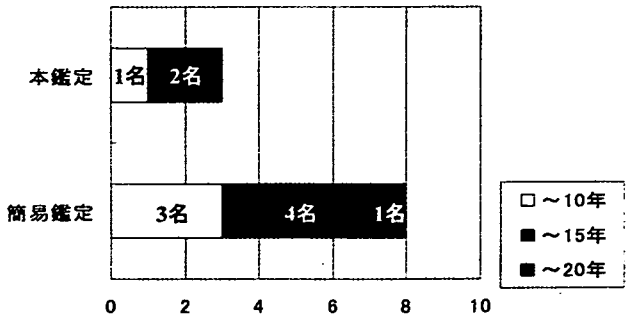

図 8　司法精神鑑定を初めて担当した時点での精神科臨床経験年数と，その鑑定種類

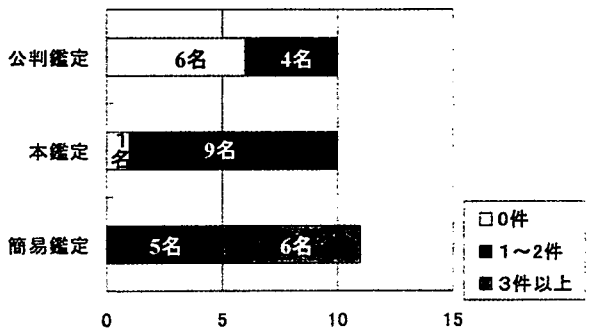

図 9　司法鑑定は年間何件引き受けることが可能と考えているか

表 1　精神鑑定を行うに際して改善すべき点

- 鑑定料が安い。
- 通常の業務を行いながら，何回も拘置所に行くため業務に支障を生ずる。
- 検察官によって調査資料が異なる。鑑定開始後に鑑定人が調査依頼をすることがある。キーパーソンの供述調書がなかったり，学籍簿がないなど情報が不足していることがある。
- 作業の効率化を図るため資料の電子化をして欲しい。
- 今後も鑑定する上で参考になるので，被鑑定人のその後の処遇に関するフィードバックをして欲しい。

表 2　司法精神医学の教育においてどのようなことが必要と思われるか

- 検察官，裁判官，医療関係者が一同に会する研修会の開催。
- 判定が難しい症例などの事例検討会の開催。
- 参考図書の紹介。
- 専門家の講演。
- 鑑定の大まかな手順（マニュアル）の作成。

表 3　司法精神医学の教育システムを確立していく上での意見

- 事例検討会を行っていくべき。
- 人間の責任能力を問う判断が要求されるため，鑑定人の人格もしっかりとしたものでなくてはならない。
- 鑑定人の判断のばらつきを抑えるため勉強会など行う必要がある。
- 司法側の対応・動きを正確に把握して，業務を適切に展開する方式を学習したい。
- 各地域ごとに司法精神医学教育センターがあれば望ましいと思う。

表 4　医療観察法についての感想

- 入院指定機関の整備をすすめるべきである。
- 鑑定入院中の身体的急変時の対応が困難。他院への受け入れの問題，離院，事故が起きた時など責任の所在はどうなるのか。身体急変時の行政の協力を切に希望する。職員の安全を考えると，保安員の配置も必要。
- 犯罪を犯した精神病者の責任を求めるか否かの二大別だけでなく，軽症例では治癒したら責任を求める制度があってもいいのではないかと思う。
- 本来，重大犯罪が医療観察法の対象であったのに現在はその他の事例にも適用されているので，検察官の意見を聞きたい。

「精神鑑定を行う際に改善すべき点」，「司法精神医学の教育においてどのようなことが必要と思われるか」，「司法精神医学の教育システムを確立していく上での意見」，「医療観察法についての感想」をそれぞれ表 1 ～表 4 に示した。精神鑑定業務を実際に担当した際，資料が不足していることを指摘する意見や，時間的な制約があるため，情報の電子化を図るなど業務を効率良く処理する対策が必要であるとの意見がみられた。司法精神医学教育に関しては，事例検討会や研修会の開催を求める意見があった。教育システムの確立に関しては，司法精神医学教育センターの設置を求める意見があり，総じて司法精神医学教育システムの確立が必要であるとする意見が多かった。

昨年から施行された医療観察法に関しては，本県で事案が実際に発生したこともあってか，鑑定入院期間中に併発した身体疾患への対応の問題や，殺人，放火，強姦，傷害致死など重大犯罪を対象とする予定であった触法行為が，それ以外の犯罪にも適用されていることへの疑問を指摘する意見もみられた。

事　例　提　示

今回，我々は，医療観察法が適用され，鑑定入院期間中に身体合併症の治療が必要になった症例を経験した。なお，この事例について，すでに前もって，我々の内の一人が簡易鑑定を担当していたことから，その鑑定結果も含めて提示する。

〈症例の概要〉 症例A，30歳代，未婚女性。Aの妊娠・出産時の状況については不明であるが，生来，知的障害があり，小学校，中学校ともに特殊学級で過ごした。中学校を卒業したAは，農作業の手伝いに2年間程従事し，その後は，知人の紹介で製造業に携わっていた。X－1年1月頃からAは，ある男性と交際を始め12月に妊娠が判明した。この時，担当医師から子宮筋腫合併妊娠であり，妊娠の継続は不可能である旨の説明を受けていたが放置していた。

X年1月，Aは傷害致死事件を起こしたため逮捕された。その後，簡易鑑定が実施され，Aは中等度精神遅滞であり，犯行時は心神耗弱の状態にあったと判断された。このため，検察側はAを起訴猶予処分とし，裁判所に医療観察法の申し立てを行い受理された。Aは直ちに医療観察法上の精神鑑定を受けるため，鑑定入院指定機関に搬送される予定であった。しかし，指定入院先が満床であったため，Aはやむなく本来は鑑定入院指定機関ではない単科の精神科病院に移送された。その数日後，他院の産婦人科医による診察が行われ，「子宮筋腫合併妊娠16週であり，妊娠を継続すると母子の生命に危険が及ぶ」と判断された。これを受け，Aが自ら人工妊娠中絶を希望したため，担当医らは，直ちにその手配を行った。しかし，触法精神障害者ということもあってか，受け入れ先の病院が見つからなかった。その後，簡易鑑定を担当していた医師らの協力により，対象者の転院が決定した。移送上の問題に関しては，関係機関に問い合わせたところ，前例がなかったこともあり，明確な回答が得られなかったため，関係機関同士で話し合い移送について検討した。その結果，転院先の医療機関までは，鑑定入院機関の責任で行い，転院先の医療機関に搬送された時点で医療観察法に基づく鑑定入院を一時執行を停止する手続きがなされた。そして，同年2月，K病院精神科に精神保健福祉法上の任意入院を適用させ身体的治療を開始した。Aは，自ら「子供をおろしてほしい」と人工妊娠中絶を希望していた。感情面では，時に流涙することもあったが，その理由については詳述できなかった。知能検査に関しては，簡易鑑定の段階で施行され，「田中ビネー知能検査　IQ：38，精神年齢6歳8カ月であり，中等度精神遅滞レベル」との結果が得られていた。入院2日目，産婦人科医師の診察を経て，再度，A本人，母親らの意思確認を行い，同意を得た上で人工妊娠中絶術を施行した。子宮筋腫に関しては，現段階では手術適応がなかったため実施しなかった。その後，出血などの合併症も認められることなく，入院5日目に退院とし，同時に検察側からAに対して再度医療観察法の鑑定入院についての告知が行われ，検察側によりAは鑑定入院先の医療機関に再移送された。

考　察

医療観察法も含めた「他害行為を行った精神障害者の処遇」の概要については，図10[7]に示したとおりであるため詳細は割愛し，本稿では，本県の精神鑑定の実状・課題と，我々が実際に経験した症例を通して医療観察法の運用上の問題提起を含めた考察を行う。

(1) 精神鑑定

本邦では，司法精神医学の研究や教育に携わる機関が乏しい[12]との指摘があるように，本県でも精神鑑定業務は一部の限られた精神科医が担当し，鑑定医は個々の臨床経験と，精神鑑定および精神科臨床の経験を積んだ上級医師による指導・助言に基づき，鑑定業務を行っているのが実状である。

精神鑑定は，これまで刑事訴訟法などに規定されている業務のみであったため，本県のような実状でも対応は可能であった。しかし，医療観察法が施行され精神鑑定業務が増加することが予想される昨今，現状のままでは一部の精神科医の負担が増えるばかりでなく，医療観察法の運用にも支障を来すことが予想される。今回のアンケート調査は，このような予見のもとに実施した。

その結果，精神鑑定業務は，鑑定件数にばらつ