Table 2 Association analysis of the 5 SNPs in males

SNP name	Allele 1/2		N	Genotype			Allele		P-value		HWE P-value
				1/1	1/2	2/2	1	2	Genotype	Allele	
rs2853550	A/G	Schizophrenia	300	4	74	222	82	518	0.68[a]	0.69	0.62
				(0.01)	(0.25)	(0.74)	(0.14)	(0.86)			
		Controls	383	7	85	291	99	667			0.82
				(0.02)	(0.22)	(0.76)	(0.13)	(0.87)			
rs1143634	A/G	Schizophrenia	298	0	24	274	24	572	0.81[a]	0.82	1.00
				(0.00)	(0.08)	(0.92)	(0.04)	(0.96)			
		Controls	383	1	27	355	29	737			0.42
				(0.00)	(0.07)	(0.93)	(0.04)	(0.96)			
rs1143633	C/T	Schizophrenia	299	59	145	95	263	335	0.43	0.47	0.81
				(0.20)	(0.48)	(0.32)	(0.44)	(0.56)			
		Controls	383	77	168	138	322	444			0.059
				(0.20)	(0.44)	(0.36)	(0.42)	(0.58)			
rs1143630	T/G	Schizophrenia	295	7	81	207	95	495	0.75	0.73	1.00
				(0.02)	(0.27)	(0.70)	(0.16)	(0.84)			
		Controls	383	6	106	271	118	648			0.32
				(0.02)	(0.28)	(0.71)	(0.15)	(0.85)			
rs16944	A/G	Schizophrenia	295	66	143	86	275	315	0.92	0.67	0.64
				(0.22)	(0.48)	(0.29)	(0.47)	(0.53)			
		Controls	385	82	186	117	350	420			0.61
				(0.21)	(0.48)	(0.30)	(0.45)	(0.55)			

(a) Calculated using Fisher's exact test.
SNP: single nucleotide polymorphism; HWE: Hardy-Weinberg Disequilibrium
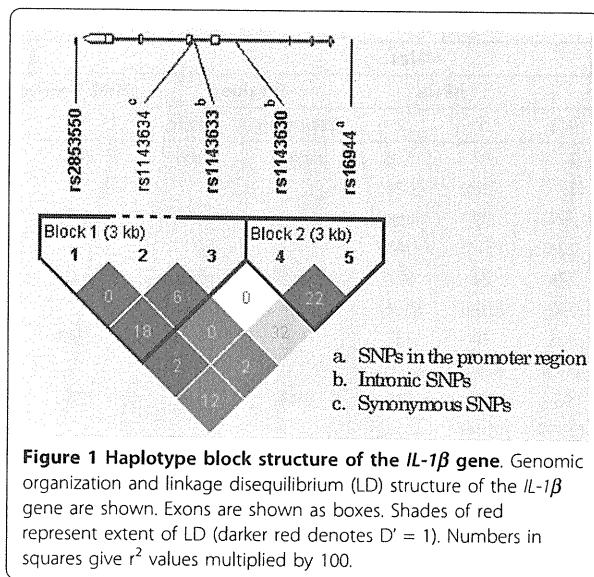Numbers in parentheses represent the frequencies of genotypes and alleles.

Table 3 Association analysis of the 5 SNPs in females

SNP name	Allele 1/2		N	Genotype			Allele		P-value		HWE P-value
				1/1	1/2	2/2	1	2	Genotype	Allele	
rs2853550	A/G	Schizophrenia	231	5	54	172	64	398	0.18	0.096	0.78
				(0.02)	(0.23)	(0.74)	(0.14)	(0.86)			
		Controls	732		7	147	578		161	1303	0.57
				(0.01)	(0.20)	(0.79)	(0.11)	(0.89)			
rs1143634	A/G	Schizophrenia	227	1	17	209	19	435	0.46[a]	0.84	0.32
				(0.00)	(0.07)	(0.92)	(0.04)	(0.96)			
		Controls	738	1	63	674	65	1411			1.00
				(0.00)	(0.09)	(0.91)	(0.04)	(0.96)			
rs1143633	C/T	Schizophrenia	225	52	104	69	208	242	0.013	**0.0073**	0.29
				(0.23)	(0.46)	(0.31)	(0.46)	(0.54)			
		Controls	740	111	357	272	579	901			0.76
				(0.15)	(0.48)	(0.37)	(0.39)	(0.61)			
rs1143630	T/G	Schizophrenia	225	6	59	160	71	379	0.97	0.83	0.80
				(0.03)	(0.26)	(0.71)	(0.16)	(0.84)			
		Controls	736	18	190	528	226	1246			0.89
				(0.02)	(0.26)	(0.72)	(0.15)	(0.85)			
rs16944	A/G	Schizophrenia	226	57	110	59	224	228	0.11	0.032	0.69
				(0.25)	(0.49)	(0.26)	(0.50)	(0.50)			
		Controls	726	144	348	234	636	816			0.50
				(0.20)	(0.48)	(0.32)	(0.44)	(0.56)			

(a) Calculated using Fisher's exact test.
SNP: single nucleotide polymorphism; HWE: Hardy-Weinberg Disequilibrium
Numbers in parentheses represent the frequencies of genotypes and alleles. Significant P-values (< 0.013) are shown in boldface.

Figure 1 Haplotype block structure of the *IL-1β* gene. Genomic organization and linkage disequilibrium (LD) structure of the *IL-1β* gene are shown. Exons are shown as boxes. Shades of red represent extent of LD (darker red denotes D' = 1). Numbers in squares give r^2 values multiplied by 100.

schizophrenia susceptibility in Asian populations, which is consistent with the previous Asian findings [21-23]. However, there was a trend of association of rs16944, in

the opposite direction to that of the Caucasians, with schizophrenia susceptibility in female subjects. Therefore, there remains a possibility that a larger study would yield a significant difference between Japanese female schizophrenic patients and controls in the allele frequency of rs16944.

A number of genome-wide association studies (GWAS) have searched for polymorphisms associated with schizophrenia [38-43]. Although no evidence of association with *IL-1β* gene has been reported, common risk alleles in the major histocompatibility region on chromosome 6, which is involved in the immune response, have shown statistically significant evidence of association [38-40]. Furthermore, a genome-wide pharmacogenomic study has shown that *IL-1α* rs11677416, which is in weak LD with rs1143633 (r^2 = 0.094, D' = 0.809 based on HapMap Japanese and Han Chinese population data, release 22), was associated with response of neurocognitive symptoms to antipsychotic treatment [44]. These findings, together with ours, suggest genetic influence on immune alterations in schizophrenia.

A shift towards the T helper type 2 (Th2) system has been indicated in schizophrenia [45-47]. IL-1β stimulates

Table 4 Haplotype analysis of *IL-1β* gene polymorphisms

Block	Haplotype	Diagnosis	Males					Females				
			Carrier	Non-carrier	χ2	Nominal P value	Permutation P value	Carrier	Non-carrier	χ2	Nominal P value	Permutation P value
	GT	Schizophrenia	336.3	265.7	0.557	0.456	0.957	251.0	213.0	6.240	0.0125	0.118
			(0.559)	(0.441)				(0.541)	(0.459)			
		Controls	447.9	326.1				901.0	585.0			
			(0.579)	(0.421)				(0.606)	(0.394)			
1	GC	Schizophrenia	183.1	418.9	0.216	0.642	0.995	149.0	315.0	2.298	0.130	0.691
			(0.304)	(0.696)				(0.321)	(0.679)			
		Controls	226.4	547.6				422.5	1063.5			
			(0.293)	(0.707)				(0.284)	(0.716)			
	AC	Schizophrenia	82.6	519.4	0.215	0.643	0.995	63.7	400.3	3.281	0.0701	0.461
			(0.137)	(0.863)				(0.137)	(0.863)			
		Controls	99.6	674.4				158.5	1327.5			
			(0.129)	(0.871)				(0.107)	(0.893)			
	GG	Schizophrenia	321.4	280.6	0.154	0.694	0.996	231.2	228.8	5.012	0.0252	0.207
			(0.534)	(0.466)				(0.503)	(0.497)			
		Controls	422.6	353.4				837.4	652.6			
			(0.545)	(0.455)				(0.562)	(0.438)			
2	GA	Schizophrenia	183.5	418.5	0.040	0.841	1.00	156.4	303.6	5.326	0.0210	0.178
			(0.305)	(0.695)				(0.340)	(0.660)			
		Controls	232.7	543.3				422.8	1067.2			
			(0.300)	(0.700)				(0.284)	(0.716)			
	TA	Schizophrenia	97.1	504.9	0.081	0.776	0.999	72.4	387.6	0.027	0.869	1.00
			(0.161)	(0.839)				(0.157)	(0.843)			
		Controls	120.7	655.3				229.8	1260.2			
			(0.156)	(0.844)				(0.154)	(0.846)			

Numbers in parentheses represent the frequencies of haplotypes. Permutation P values were based on 10,000 permutations.

the production of prostaglandin E2, which is an important cofactor for the induction of T-helper lymphocyte activity towards Th2 direction. Significant increase in circulating mRNA expression levels of IL-1β has been observed in schizophrenic patients [9]. The changes in mRNA levels may reflect the genetic variation in *IL-1β* gene. The findings on biological roles of *IL-1β* polymorphisms, however, have not been consistent across studies. A/A genotype of rs16944 has been associated with higher gastric mucosa IL-1β levels in H. pylori positive population [48]. On the other hand, subjects with G/G genotype showed an increased release of IL-1β from mononuclear cells after stimulation with lipopolysaccharide [49]. Recent studies suggest that the functional role of rs16944 may depend on the *IL-1β* promoter region haplotypes including rs16944 and rs1143627 [50-53]. Although the findings are inconsistent, these previous studies suggest that rs16944 could affect the expression levels of IL-1β. On the other hand, the influence of rs1143633 on IL-1β expression levels has not been previously reported.

Intriguingly, rs1143633 and rs16944 have also been associated with cortisol response to dexamethasone in healthy subjects [30]. Alleles associated with increased cortisol response to dexamethasone were shown to be associated with schizophrenia in the present study. Higher rates of non-suppression to dexamethasone compared to healthy subjects have been reported in schizophrenia [54] and schizotypy [55]. On the other hand, Ismail et al [56] reported that less than 2% of their schizophrenic patients were non-suppressors. Although the findings are inconsistent, these studies indicate that schizophrenia may be associated with alteration in hypothalamic- pituitary- adrenal (HPA) axis. Taken together, our findings suggest that *IL-1β* gene polymorphisms may play a role in the HPA axis alteration in schizophrenic patients.

Our results showed significant association of rs1143633 with schizophrenia in only females. Although our male sample was not large enough to detect a small relative risk, our data suggest that susceptibility to schizophrenia is more influenced by the *IL-1β* gene variation in females. To our knowledge, no previous studies have examined the gender differences in the association between *IL-1β* gene polymorphisms and schizophrenia. However, gender differences have been reported in the association between schizophrenia and RELA gene [27] encoding the major component of NF-κB, which is activated by IL-1β. Taken together with our results, the influence of IL-1β on susceptibility to schizophrenia may differ between genders. Indeed, gender differences in immunity have been reported in previous studies [36]. IL-1 release from mononucleated cells has been shown to be menstrual phase dependent in females and lower in males [57].

Furthermore, in vitro stimulation of lymphocytes with phytohemagglutinin has shown that females produce more Th2 cytokines than males [58]. Thus, future studies investigating associations of immune-related genes with schizophrenia should take into consideration the possible gender differences.

There are some limitations to this study. The ethnicity of the participants was based on self-reports and was not confirmed by genetic analyses. Our positive results might be derived from sample bias due to population stratification, although the Japanese are a relatively homogeneous population. Furthermore, structured interview such as SCID (Structured Clinical Interview for DSM) was not used for diagnosis in this study. Finally, the function of the *IL-1β* gene SNPs are unclear. Future studies are necessary to elucidate the function and its relationship with the pathogenesis of schizophrenia.

Conclusions

Our results suggest that rs1143633 of *IL-1β* gene is associated with schizophrenia susceptibility in a Japanese population and that the influence of *IL-1β* gene variations on susceptibility to schizophrenia may be greater in females than in males. We obtained no significant evidence for a well-studied polymorphism rs16944 being associated with schizophrenia, which is consistent with previous studies in Asian populations. However, a trend of higher A allele frequency of rs16944 in female patients with schizophrenia leaves open a possibility that a larger study may yield a significant difference. The results of the present study provide further support for the role of IL-1β in the etiology of schizophrenia. Future studies are warranted to replicate the present findings and to reveal the functional role of *IL-1β* gene in pathophysiology of schizophrenia.

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Authors' contributions

DS and HK designed the study and DS wrote the draft of the manuscript. DS, HH, TT, KH, MO, MT, and HK made the diagnosis according to DSM-IV criteria. DS, HH, TT, KH, MO, and HK screened the healthy participants using the Mini International Neuropsychiatric Interview (M.I.N.I.). DS and YI performed the genotyping. HK supervised the data analysis and writing of the paper. TH and NA also supervised the writing of the paper and gave critical comments on the manuscript. All authors contributed to and have approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Expert consensus on hospitalization for assessment: a survey in Japan for a new forensic mental health system

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Abstract

Background: In Japan, hospitalization for the assessment of mentally disordered offenders under the Act on Medical Care and Treatment for the Persons Who Had Caused Serious Cases under the Condition of Insanity (the Medical Treatment and Supervision Act, or the MTS Act) has yet to be standardized.

Methods: We conducted a written survey that included a questionnaire regarding hospitalization for assessment; the questionnaire consisted of 335 options with 9 grades of validity for 60 clinical situations. The survey was mailed to 50 Japanese forensic mental health experts, and 42 responses were received.

Results: An expert consensus was established for 299 of the options. Regarding subjects requiring hospitalization for assessment, no consensus was reached on the indications for electroconvulsive therapy (ECT) or for confronting the offenders regarding their offensive behaviors.

Conclusions: The consensus regarding hospitalization for assessment and its associated problems were clarified. The consensus should be widely publicized among practitioners to ensure better management during the hospitalization of mentally disordered offenders for assessment.

Background

The need to establish a sophisticated forensic mental health system has increased as a result of the global trend toward the deinstitutionalization of patients with mental disorders [1]. However, for many years, Japan had no specific legal provisions for offenders with mental disorders [2]. Once such offenders were entrusted into the mental health system, they were treated under the Mental Health and Welfare (MHW) Law and were completely detached from the criminal justice system [3].

In 2005, the forensic mental health system in Japan underwent reform along with the enforcement of the Act on Medical Care and Treatment for the Persons Who Had Caused Serious Cases under the Condition of Insanity: the Medical Treatment and Supervision Act (MTS Act) [4]. Under this new system, a person who commits a

serious criminal offense while in a state of insanity or with diminished responsibility is be treated and supervised in a judicial administrative frame. The public prosecutor makes allegations to the District Court for the purpose of judgment. The judgment panel consists of one judge and one mental health reviewer ('seishin-hoken-shinpan-in'), with the latter being selected from a group of psychiatrists who hold Judgment Physician license ('seishin-hoken-hantei-i' a national license for forensic mental health specialists). The panel can arrive at three possible verdicts: an order to hospitalize the offender for medical treatment, an order to care for the offender as an outpatient in the community, or a no-treatment order. The offender is then obligated to accept the special psychiatric care supplied by the designated medical facilities and to submit to continuous supervision by a Rehabilitation Coordinator ('shakai-fukki-chousei-kan') working in a probation office.

To return a correct verdict, the MTS Act requires a psychiatric examination. The three essential factors that

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must be examined when making a treatment order decision are the nature and severity of the mental disorder and its relationship to the offense, the offender's 'treatability' or responsiveness to psychiatric treatment, and the factors that could hinder the person's rehabilitation and the likelihood of a second offense. The offender should be hospitalized for 2 to 3 months during the psychiatric examination, while continuing an appropriate course of psychiatric treatment; this hospitalization period for assessment is known as 'kantei-nyuin' [5].

In 2008, the Japanese Government published a list of 239 Japanese mental hospitals (1.9 per 1,000,000 of the population) for the purpose of hospitalization for assessment of mentally disordered offenders [6]. However, the criteria used to select these facilities are vague.

The MTS Act hardly regulates even the minimum requirements for these facilities. Therefore, remarkable variations exist in the hospitalization conditions for these patients, such as in the availability of human resources, the diagnostic and therapeutic strategies in use, the attitudes regarding ethical issues, and the physical facilities themselves. It had been reported that about 60% to 80% of psychiatrists who treat offenders in designated inpatient facilities find problems with the written reports of psychiatric examinations conducted and written at the assessment stage [7]. In addition, while it is recommended that offenders be treated by a multiple disciplinary team (MDT) similar to that used for regular acute psychiatric care [8], this recommendation was not known at 14% of the facilities that were surveyed [9].

To minimize the variation, and to improve the quality of the assessment, we conducted a written survey that was delivered by mail to leading Japanese forensic mental health experts, and clarified the expert consensus regarding hospitalization for assessment.

Methods
Creating the surveys
To create the questionnaire, we formed a working team comprised of judgment physicians, psychiatrists with experience conducting psychiatric examinations, and doctors belonging to facilities for hospitalizations and assessment of mentally disordered offenders. Then, we attempted to extract suitable questionnaire items, which we classified as general introductory questions regarding the characteristics of the facilities (including sections on the 'Structure' and 'Staff') or detailed questions regarding management (including sections on 'Items Before the Start of Examination', 'Diagnosis and Treatment', 'Issues Regarding Informed Consent and Forced Treatment', 'Judgment', and 'Hypothetical Clinical Situations'). We also referred to reviews in the literature to extract questions [7,10]. We then collected the opinions of several experts in an exploratory committee examining

'Research on the Improvement of the System of Hospitalization for Assessment' and revised the questionnaire. Using the above-described procedure, we developed a 60-question survey with 335 options. A sample of the questions is presented in Table 1.

Rating scale
For the 335 options in the survey, we asked the experts to evaluate the appropriateness of the option using a 9-point scale that was slightly modified from the format developed by the RAND Corporation for ascertaining expert consensus. To develop this rating scale, we referred to the expert consensus guideline series developed by Expert Knowledge Systems, LLC [10]. The anchors of the rating scale are presented in Appendix 1.

Composition of the expert panel
We identified 50 leading Japanese experts on forensic mental health, focusing on those individuals with extensive experience managing hospitalizations for assessment under the MTS Act. The experts were identified based on their published research in this area and/or their participation in the Japanese Society of Forensic Mental Health or a related association.

Ethical issues
We reported the contents of this survey to the Ethical Council of the Graduate School of Medicine at Chiba University in advance, and the council declared that the survey did not pose any ethical problems. All the experts were given a written explanation of the purpose of the survey. All respondents provided their informed written consent to participate in the study.

Data analysis for options scored on the rating scale
For each option, we first defined the presence or absence of a consensus as a distribution unlikely to occur by chance by performing a χ^2 test ($P < 0.05$) of the distribution of the scores across three ranges of appropriateness (7-9: appropriate; 4-6: unclear; 1-3: inappropriate). Next, we calculated the mean and 95% confidence interval (CI). A categorical rating of first-line, second-line, or third-line options was designated based on the lowest category in which the CI fell, with boundaries of 6.5 or greater for first-line (preferred) options, 3.5 or greater but less than 6.5 for second-line (alternate) options, and less than 3.5 for third-line (usually inappropriate) options. Among the first line options, we defined an option as 'best recommendation/ essential' if at least 50% of the experts rated it as 9. This analysis method was adopted after reference to an expert consensus guideline series [10].

Additionally, we extracted all the items included in the present questionnaire that were also used in a previous

Table 1 Sample of the survey questions

Please evaluate the following options for interventions with a subject who refuses to take medication because of a lack of insight into his or her psychiatric disorder, but who is not seriously aggressive

(1) Explanation and persuasion	1 2 3	4 5 6	7 8 9
(2) Forced medication using liquid or oral disintegrating drugs	1 2 3	4 5 6	7 8 9
(3) Forced intravenous or intramuscular injection	1 2 3	4 5 6	7 8 9
(4) Forced depot injection	1 2 3	4 5 6	7 8 9
(5) Masked medication	1 2 3	4 5 6	7 8 9
(6) Electroconvulsive therapy	1 2 3	4 5 6	7 8 9
(7) Forced medication using a nasal tube	1 2 3	4 5 6	7 8 9

questionnaire survey [7] to collect the general opinions of forensic psychiatrists. We then compared the two sets of results to justify the present survey by evaluating the differences between the expert consensus and the general opinion of forensic psychiatrists.

Results

Response rate

We received responses from 42 (84%) of the 50 experts to whom the survey was sent. Two of the respondents were female and the rest were male. Of the 42, 2 were professors in the psychiatric department of a university, 14 belonged to a national hospital, 20 belonged to a prefectural hospital, and 6 belonged to a private hospital. All the respondents held a national license as a Designated Physician ('seishin-hoken-shitei-i') under the MHW Law and Judgment Physician in the MTS Act. Furthermore, all the respondents were over 35 years of age and had at least 10 years of experience in psychiatric practice.

All 42 responders answered all the questions adequately. No doubts or criticisms regarding the questionnaire were noted by the experts.

Degree of consensus

Of the 335 options rated using the 9-point scale, a consensus was reached for 299 (89.3%) options, as defined by the presence of statistical significance using a χ^2 test.

A total of 113 options were defined as first-line options, of which 29 options were defined as 'best recommendation/essential'. In all, 109 options were defined as second-line options. The remaining 77 options were defined as third-line or usually inappropriate options (see Figure 1).

Structure

This section consisted of six questions aimed at determining the necessary resources for the appropriate administration of hospitalizations for assessment.

As facilities for the hospitalized assessment of mentally disordered offenders, the best recommendation of

the experts was the National Center Hospital, National Center for Neurology and Psychiatry (NCH-NCNP) (mean 8.07; 95% CI 7.62 to 8.53) or an establishment with a specialized facility for the exclusive use of psychiatric examinations (mean 8.03; 95% CI 7.53 to 8.52). For psychiatric examinations, a psychiatric emergency ward (mean 7.61; 95% CI 7.1 to 8.12) or, as a minimum requirement, a psychiatric acute-phase care unit (mean 7.45; 95% CI 6.77 to 7.58) were recommended as first-line options. Medical examination rooms with multiple exit doors (mean 7.64; 95% CI 7.19 to 8.1) were recommended. To prevent self-hanging, a shower without a hose in each bedroom (mean 7.24; 95% CI 6.8 to 7.68) was recommended. As for patient amenities, a television (mean 7.07; 95% CI 6.57 to 7.58) and newspapers (mean 7.26; 95% CI 6.76 to 7.76) were recommended.

Staff

In this section, we addressed the need for human resources using 16 questions. The participation of Judgment Physicians (mean 8.29; 95% CI 7.93 to 8.54) and
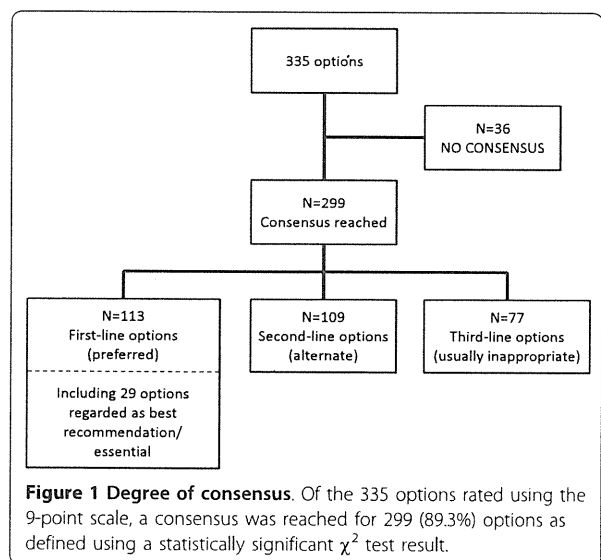

Figure 1 Degree of consensus. Of the 335 options rated using the 9-point scale, a consensus was reached for 299 (89.3%) options as defined using a statistically significant χ^2 test result.

Designated Physicians (mean 8.24; 95% CI 8.01 to 8.56) in the hospitalization process was deemed essential. At least 1 staff nurse per 10 inpatients in the assessment ward (mean 7.10; 95% CI 6.56 to 7.64) was recommended. The participation of psychiatric social workers (mean 8.24; 95% CI 7.88 to 8.66) and psychotherapists (mean 8.29; 95% CI 7.87 to 8.7) was also deemed essential. The participation of occupational therapists (mean 7.57; 95% CI 7.07 to 8.07) was recommended. However, a consensus was not reached on whether psychiatric social workers or occupational therapists should be involved in the writing of the examination report.

The formation of an MDT for the psychiatric examination (mean 7.62; 95% CI 7.15 to 8.09) was recommended. However, a consensus was not reached on whether the team should include pharmacists and dietitians or how often the team meetings should be held.

In cases of hospitalization for assessment, the court appoints a case examiner. It was recommended that the examiner not participate in the treatment of the subject directly, but rather that the examiner discusses the treatment strategy with the physician in charge of the subject from time to time (mean 7.17; 95% CI 6.67 to 7.66). In cases where the examiner and the physician in charge disagreed regarding the treatment strategy, the experts did not agree on a first-line option but recommended that the examiner and physician in charge continue their discussion (mean 6.61; 95% CI 5.95 to 7.27). They also recommended that the final decision regarding treatment should be made by the physician in charge (mean 6.56; 95% CI 6.05 to 7.07).

Items before the start of examination

This section addressed the procedure for accepting offenders to be examined, along with some other institutional issues, and consisted of six questions.

When consulted regarding the acceptance of an offender requiring hospitalization for assessment, the experts did not show any particular first-line options regarding the provision of advance information about the offender. Instead, they preferred to use the offender's category of offense (mean 6.48; 95% CI 5.69 to 7.27) when deciding on either the acceptance or rejection of an offender.

The issue of whether or not medical students should participate in the hospitalization for assessment process did not reach consensus.

Diagnosis and medical treatment

This section contained questions regarding basic approaches for managing subjects and consisted of six questions.

An interview with the subject (mean 8.55; 95% CI 8.28 to 8.82) and the checking of vital signs (mean 8.74; 95% CI 8.59 to 8.89) on the first day of admission were deemed essential. A family interview (mean 8.55; 95% CI 8.25 to 8.84), consultation with the rehabilitation coordinator in the probation office (mean 8.50; 95% CI 8.22 to 8.78), blood exams (mean 8.81; 95% CI 8.67 to 8.95), intelligence tests (mean 8.43; 95% CI 8.19 to 8.67), personality tests (mean 8.26; 95% CI 7.96 to 8.56) and electroencephalograms (mean 8.21; 95% CI 7.9 to 8.52) performed during the hospitalization period were all deemed as essential. A brain magnetic resonance imaging (MRI) examination (mean 7.40; 95% CI 6.93 to 7.88) was also recommended.

Regarding medication, the prescription of medications to the offenders in the same manner as for other patients with mental disorders (mean 8.24; 95% CI 7.95 to 8.53) was recommended. Regarding psychotherapy, supportive psychotherapy (mean 7.85; 95% CI 7.43 to 8.27) consisting of rapport (mean 7.68; 95% CI 7.16 to 8.2) and psychoeducation (mean 7.22; 95% CI 6.69 to 7.75) were recommended as first-line options.

Issues regarding informed consent and forced treatment

This section contained eight questions regarding core ethical problems and systematic issues associated with involuntary hospitalization.

The experts recommended that every possible effort to be made to obtain informed consent from the offenders but that the necessary treatment should be enforced upon the patient if consent was not obtained (mean 7.51; 95% CI 7.15 to 7.88). During hospitalization, the need for seclusion or restrictions should be evaluated on a flexible basis (mean 7.52; 95% CI 7 to 8.05), and even if seclusion is decided upon, once the subject has calmed down, the experts recommended that the day-room be made available to the subjects for a limited time (mean 7.93; 95% CI 7.66 to 8.2) and/or under the observation of the medical staff (mean 7.93; 95% CI 7.62 to 8.24). Seclusion and restriction were to be considered in situations where direct violence to other patients (mean 8.31; 95% CI 8.03 to 8.59), violent behavior or threats of violence towards the staff (mean 7.81; 95% CI 7.49 to 8.13), destroying equipment in the ward (mean 7.81; 95% CI 7.46 to 8.16), clear attempts at suicide (mean 8.19; 95% CI 7.89 to 8.49), or impulsive self-destructive behavior (mean 7.57; 95% CI 7.19 to 7.95) were possibilities.

Judgment

A panel must judge the acts of the offender and deliver a verdict. This section concerned the judgment process and consisted of four questions.

The experts recommend that the offender's own motivation to recover over the course of hospitalization be carefully evaluated (mean 7.69; 95% CI 7.26 to 8.13). Even after the completion of the psychiatric

examination, the continuation of maintenance therapy (mean 8.12; 95% CI 7.69 to 8.55) or therapy to improve his/her mental status (mean 7.05; 95% CI 6.56 to 7.54) until the time of the final judgment was recommended. If the status of the subject changed, leading to a reconsideration of the diagnosis once the results of the psychiatric examination had been reported, a quick report to the panel (mean 8.22; 95% CI 7.87 to 8.53) was essential.

Hypothetical clinical situations

This section covered several situations that have yet to be adequately addressed in Japan and consisted of 14 questions.

When examining a subject who has committed a homicide, who does not exhibit any obvious psychotic symptoms, and whose past history is unknown, the experts recommend careful observation without medication for a number of days (mean 7.07; 95% CI 6.58 to 7.57).

Regarding the treatment of a subject who refuses to take medication because of a lack of insight into his or her psychiatric disorder, but who is not seriously

aggressive (see Figure 2), the experts recommended that only explanation and persuasion be used as treatment options (mean 7.93; 95% CI 7.56 to 8.27).

Regarding the topic of confronting the subject about his or her offense, the experts did not reach a consensus (see Figure 3); they did not recommend avoiding any mention of the offense (mean 2.81; 95% CI 2.31 to 3.31).
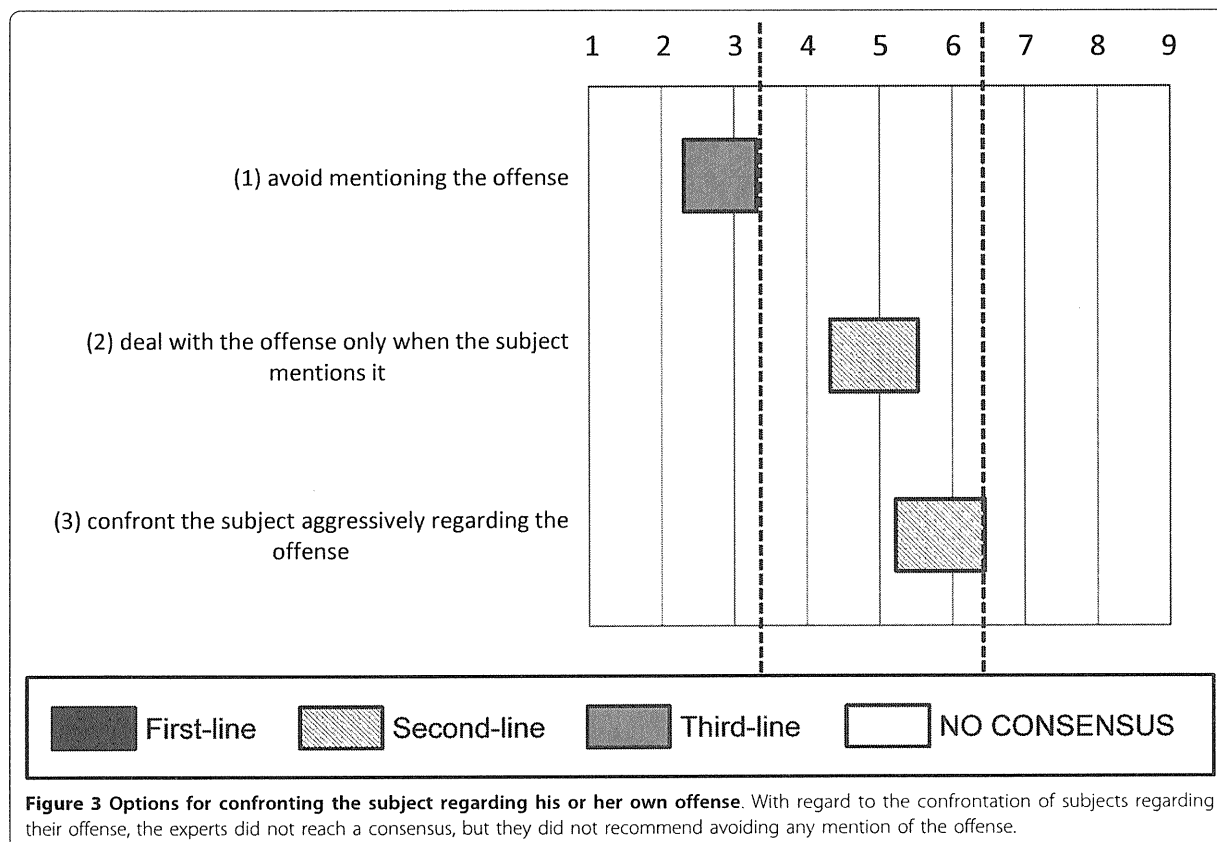
The experts did not necessarily approve of the use of electroconvulsive therapy (ECT) if the offender refused to eat or take drugs because of suicidal thoughts (see Figure 4) or after a neuroleptic malignant syndrome caused by previous medications (see Figure 5).

Comparison of expert consensus and general opinions of forensic psychiatrists

Five items were identified as having the same content as questions included in a past questionnaire survey examining the general opinions of forensic psychiatrists.

In the staff section, regarding the relationship between the case examiner and the physician in charge, 39 of the 105 respondents (37.1%) in the previous survey chose the option 'the case examiner should also be the

Figure 2 Options for interventions for subjects who refuse therapy. With regard to interventions for subjects who refuse to take medication because of a lack of insight into their psychiatric disorder but who are not seriously aggressive, the experts recommend explanation and persuasion.

Figure 3 Options for confronting the subject regarding his or her own offense. With regard to the confrontation of subjects regarding their offense, the experts did not reach a consensus, but they did not recommend avoiding any mention of the offense.

physician in charge'. This option did not reach a consensus (mean 4.60; 95% CI 3.85 to 5.34) in the present survey. Only 12 of the 42 experts (28.6%) marked this option as being appropriate. However, the percentage of participants who marked this option as being appropriate was not statistically different between the two surveys (Fisher's exact test, $P = 0.32$).

In the diagnosis and medical treatment section, 67 of the 105 respondents (63.8%) in the previous survey chose the option 'to prescribe medications for the offenders in the same way as they would other patients with mental disorders'. As described above, this option reached consensus (mean 8.24; 95% CI 7.95 to 8.53) in the present survey. Of the 42 experts, 40 (95.2%) marked this option as being appropriate. The percentage of participants who marked this option as being appropriate was significantly different between the two surveys (Fisher's exact test, $P < 0.001$).

Regarding issues concerning informed consent and forced treatment, 20 of the 105 respondents (19.0%) in the previous survey chose the option 'continue seclusion (for 1 week or more) even if the offender has calmed down'. This option was not supported by experts (mean 2.14; 95% CI 1.74 to 2.54) in the present survey. None

of the experts marked this option as being appropriate. The percentage of participants who marked this option as being appropriate differed significantly between the two surveys (Fisher's exact test, $P < 0.01$).

Regarding hypothetical clinical situations, 33 of the 107 respondents (30.8%) in the previous survey selected the option 'confront the subject regarding his or her offense aggressively'. The experts defined this option as an alternate treatment (mean 5.83; 95% CI 5.22 to 6.45) in the present survey. Of the 42 experts, 16 (38.1%) marked this option as being appropriate. The percentage of participants who marked this option as being appropriate was not significantly different between these two surveys (Fisher's exact test, $P = 0.40$). Regarding the use of ECT, 57 of 105 respondents (54.3%) in the previous survey chose the option 'electroconvulsive therapy should not be performed during the assessment process'. This option did not reach a consensus (mean 5.14; 95% CI 4.34 to 5.95) in the present survey. Of the 42 experts, 16 (38.1%) marked this option as being appropriate. The percentage of participants who marked this option as being appropriate was not significantly different between these two surveys (Fisher's exact test, $P = 0.08$).

The above results are summarized in Table 2.

Figure 4 Options regarding the indications for electroconvulsive therapy (ECT) among subjects who refuse to eat. The experts did not necessarily approve of the use of electroconvulsive therapy if the subject refused to eat or take drugs because of suicidal thoughts.
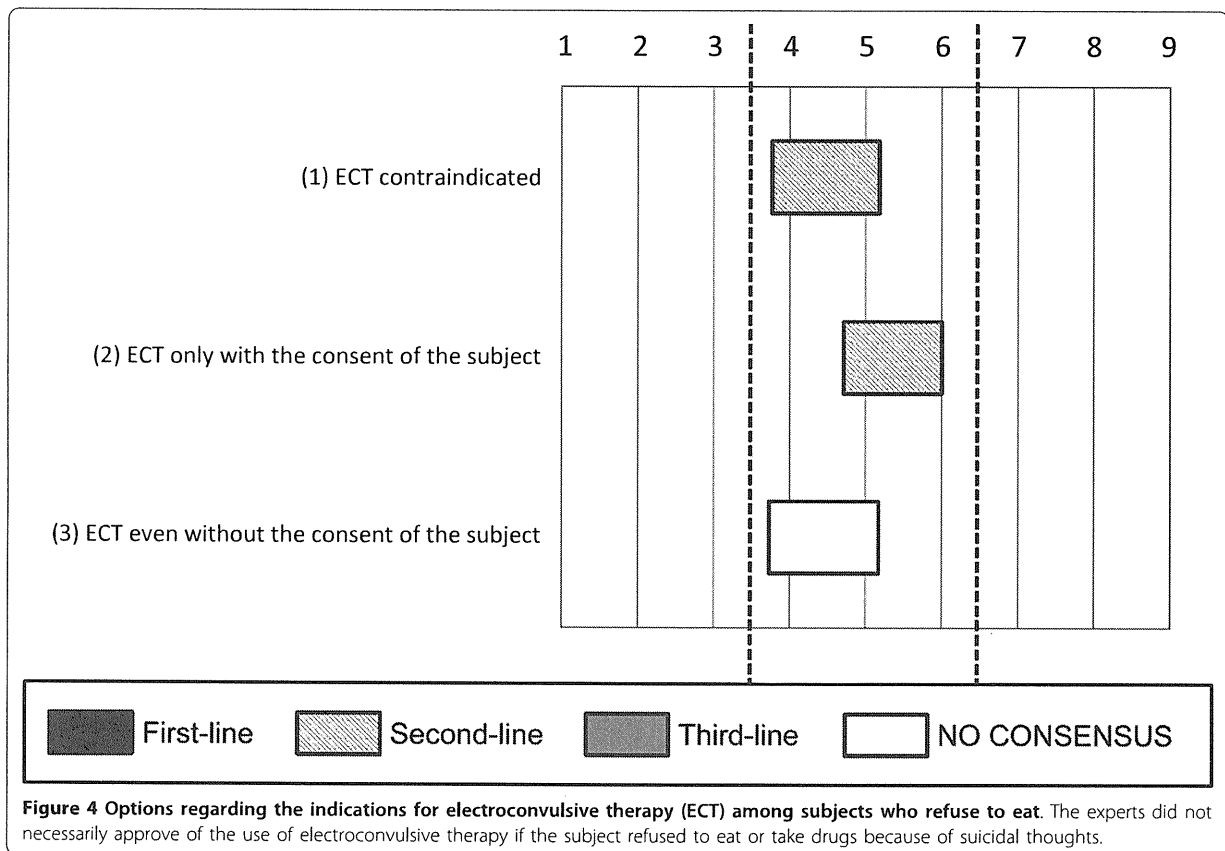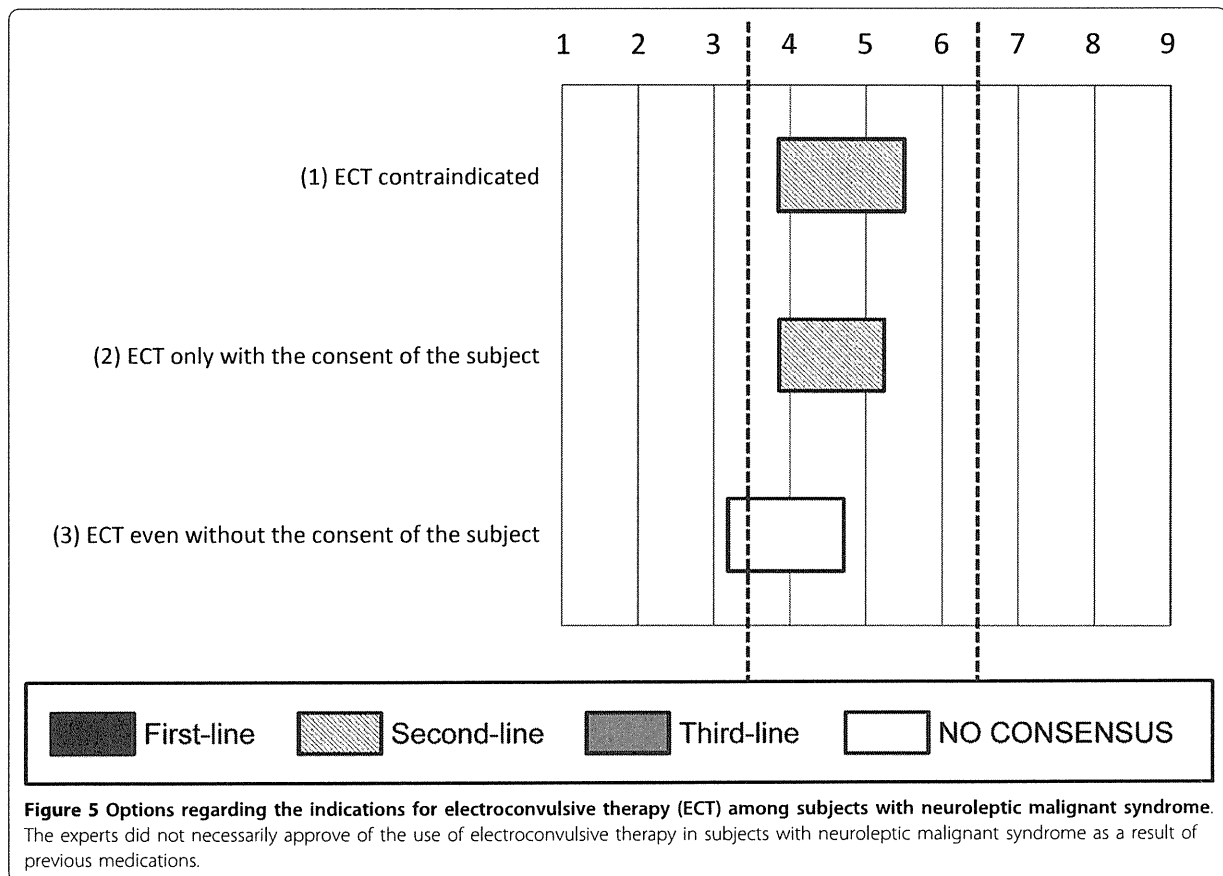
Discussion

In the present study, we distributed a written survey to Japanese forensic mental health experts concerning hospitalization for assessment under the new forensic mental health system in Japan. An expert consensus was established for 299 of the 335 options. The results clarified the expert consensus and the current problems associated with the hospitalization for assessment system.

The purpose of hospitalization for the assessment of offenders with mental disorders who have committed serious crimes is to determine the nature and severity of the mental disorder and its relationship to the act, the subject's 'treatability' or responsiveness to psychiatric treatment, and the factors expected to hinder the person's rehabilitation, enabling their best management [4]. Therefore, adequate security is necessary, along with high-quality medical care that includes a well developed infrastructure and staff at the assessment facility.

Regarding infrastructure, the majority of experts named the NCH-NCNP and a specialized facility exclusively dedicated to psychiatric examinations as the best options for use as an assessment facility. Designated medical facilities for inpatient treatment that have been

newly established by the MTS act are well equipped for both the security and comfort of the patients. Whether detailed brain imaging systems that are not available at all facilities, such as positron emission tomography or single photon emission computed tomography, are necessary for all offenders subjected to a hospitalization for assessment remains uncertain. Nonetheless, subjects with suspicious organic brain syndromes, including dementia, who exhibit behavioral and psychological symptoms have been reported [11]. Brain-imaging systems may be necessary for the accurate diagnosis of these subjects. Indeed, the experts selected MRI as a first-line option for necessary equipment. A facility that specializes exclusively in psychiatric examinations should be equipped with these machines in addition to the capability of providing adequate security equal to that of a designated medical facility for inpatient treatment.

Regarding staff, the experts claimed that the participation of the Judgment Physicians and the Designated Physicians in the activities at the assessment facility was essential. For appropriate psychiatric examinations, they also recommended that a relatively high nursing staff ratio of 1 nurse for every 10 subjects be adopted. The

Figure 5 Options regarding the indications for electroconvulsive therapy (ECT) among subjects with neuroleptic malignant syndrome. The experts did not necessarily approve of the use of electroconvulsive therapy in subjects with neuroleptic malignant syndrome as a result of previous medications.

ratio of 1 nurse per 10 subjects is nearly equal to that in most psychiatric acute-phase care units in Japan and similar to that in the US and Italy but lower than that of specialized forensic psychiatric wards in England, The Netherlands or Japan [12]. Psychiatric social workers and psychotherapists were also deemed essential. The participation of occupational therapists was also recommended. These results suggest that the subjects' behavior, including their interpersonal actions and their responses to medical treatment, should be evaluated by an MDT using intensive psychotherapeutic approaches

under minimal seclusions or restrictions. Nonetheless, the majority of facilities performing hospitalizations for assessment are not equipped with psychiatric emergency wards or psychiatric acute-phase care units with access to these necessities [7]. Thus, many psychiatric examinations appear to be performed in inadequate environments, potentially resulting in serious problems.

Regarding psychiatric examinations during the period of hospitalization, family interviews, consultation with Rehabilitation Coordinators in the probation office, typical laboratory medical examinations, intelligence tests,

Table 2 Differences between general opinion and expert consensus

Option	Rate of appropriateness		P value
	General	Experts	
The case examiner should also be the physician in charge	39/105 (37.2%)	12/42 (28.6%)	NS
Medications should be prescribed to offenders in the same manner as they would be for other patients with mental disorders	67/105 (63.8%)	40/42 (95.2%)	<0.001
Continue seclusion (for 1 week or more) even if the offender calms down	20/105 (19.0%)	0/42 (0%)	<0.01
Confront the subject aggressively regarding his or her offense	33/107 (30.8%)	16/42 (38.1%)	NS
Electroconvulsive therapy should not be used during the assessment process	57/105 (54.3%)	16/42 (38.1%)	NS

P values were assessed by Fisher's exact test.
NS = not significant.

personality tests, and electroencephalograms were deemed essential. Regarding the individuals who should be responsible for writing the examination reports, Judgment Physicians, Designated Physicians and psychotherapists were deemed as being essential to the reporting process, but a consensus was not reached regarding psychiatric social workers or occupational therapists.

Regarding the treatment of the subject during the process, the consensus was that the examiner appointed by the court must not directly treat the subject, but rather should discuss the treatment strategy with the physician in charge of the subject from time to time. If the opinions of the examiner and the physician in charge were conflict regarding the treatment strategy, the experts did not agree on a first-line option, but recommended that the examiner and physician in charge continue their discussion and that the final decision regarding treatment should be made by the physician in charge. The expert consensus indicated the importance of an MDT in the performance of the psychiatric examination. Since there may be a risk of a dual-role dilemma between the evaluator and the therapist if the examiner and the physician in charge are the same person [13], the examiner must not be the physician in charge of the subject [8]. However, this principle is not well known to forensic psychiatrists in Japan. A certain period of time exists between the end of the psychiatric examination and the judge's determination, and the expert consensus is that medical treatment should be continued during this time to maintain or improve the subject's mental status. These results indicate that the hospitalization for assessment system is meant not only to evaluate the offender, but also as a means of therapy.

Regarding the use of ECT, the experts' opinions varied considerably. Ethical issues regarding the use of ECT for forensic patients are often discussed [14], but some forensic subjects with mental disorders actually require ECT. Witzel reported a patient with psychotic depression who was successfully treated using ECT in a forensic psychiatric hospital, supporting the need for ECT in forensic mental health [15]. In Japan, one case report described the use of ECT for a forensic patient after the approval of an ethical council at a designated medical facility for inpatient treatment [16], although ethical councils are not always present at hospitalization for assessment facilities. Another ECT issue is the risk of amnesia, which can be an adverse effect of ECT and may complicate the accurate evaluation of the subject's mental status. At present, the Japanese research group in forensic psychiatry does not recommend the use of ECT, except in very rare situations [17]. Japanese forensic psychiatrists seem to dislike using ECT [7]. The experts also hesitated to use ECT for forensic patients. Overall, the indications for ECT during the

hospitalization for assessment process may be limited to life-threatening situations.

The experts recommended that the physician in charge make every possible effort to obtain informed consent from the subject before providing medical treatment but agreed that the necessary treatment should be forced upon the subject if consent cannot be obtained. They also recommended that the need for seclusion or restriction be carefully evaluated and that if a decision to seclude the subject is made, the subject should still be given access to the dayroom for a limited time or while under the observation of the medical staff once he or she has calmed. Above all, the experts recommended that decisions regarding forced treatment during hospitalization for assessment should be made in the same manner as those for general psychiatric treatment. However, this principle has not yet spread among forensic psychiatrists in Japan.

The decision as to whether offenders should be confronted with their own offenses during the hospitalization for assessment process is a complicated one. In forensic settings, psychiatrists often experience the dual-role dilemma of having to evaluate the offender and also act as his or her therapist [13]. In a therapeutic context, it is very important for forensic subjects to reflect on their own past behaviors, and such confrontation methods are effectively used in designated medical facilities in Japan [18,19]. However, such confrontations may create heavy burdens for both the offenders and the medical staff in the context of hospitalizations for assessment. When subjects express their emotions and ideas about their own offenses during the psychiatric examination, it may be important that the medical staff attend to the subjects' confusion and record their emotions without criticism [20].

A limitation of the present research is that the 60 question items included in the survey could not cover all the issues regarding hospitalization for assessment. Although we created the questionnaire used in the present study based on a detailed review and hearing, other problems that we did not consider may be present. Further investigation, possibly including the distribution of a second questionnaire to experts in this field, is needed in the future.

Conclusions

To the best of our knowledge, this is the first report to survey the attitudes and ideas of forensic mental health experts regarding the hospitalization for assessment process in Japan. The expert consensus about the process is summarized below. The facility should have the necessary infrastructure and human resources to perform adequate psychiatric examinations. MDTs consisting of several specialists should be formed before the start of the psychiatric examination. The examiner and the

physician in charge should discuss the treatment strategy of the subject from time to time. Interviews with the subject and his/her family members, physical and mental examinations, and also brain imaging tests should be performed. Medications and non-invasive psychotherapy are recommended just as they are for patients with acute mental disorders. Practitioners should try to obtain informed consent from the patient for all therapies whenever possible and should minimize any seclusions or restrictions. After the completion of the psychiatric examination, therapeutic approaches should continue until the subject has left the facility, and if the status of the subject changes, it should be reported quickly to the court. A consensus was not reached regarding the indications for electroconvulsive therapy and how best to confront the subject with his/her offense during the term of the hospitalization for assessment. The expert consensus differs from the general opinions of forensic psychiatrists in Japan in some aspects. Now that this expert consensus has been reached, it must be widely publicized among practitioners of forensic mental health and fine tuned through critical discussion to enable better management during the hospitalization for assessment process.

Appendix 1
Rating scale

9. The option is extremely appropriate: I always choose to adopt it.

8. The option is usually appropriate: I usually choose to adopt it.

7. The option is usually appropriate: I often choose to adopt it.

6. It is unclear whether the option is appropriate: I choose to adopt it when the situation calls for it.

5. It is unclear whether the option is appropriate: I do not know whether to choose to adopt it.

4. It is unclear whether the option is appropriate: I choose to adopt it only in rare situations.

3. The option is usually inappropriate: I do not adopt it often.

2. The option is usually inappropriate: I seldom adopt it.

1. The option is extremely inappropriate: I never adopt it.

Note: In evaluating each option, first assess which range is most applicable to the option, 'appropriate (points 7-9)' 'inappropriate (points 1-3)' or 'unclear (point 4-6)', and then choose the most applicable point in the chosen range.

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Authors' contributions
AS, MF, TN, YO, MS and MY conducted the questionnaire. AS conducted the statistical analysis. AS, MF, MI and YI wrote the manuscript. YI acted as the research administrator. All the authors have read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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Criterion and Construct Validity of the CogState Schizophrenia Battery in Japanese Patients with Schizophrenia

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Abstract

Background: The CogState Schizophrenia Battery (CSB), a computerized cognitive battery, covers all the same cognitive domains as the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery but is briefer to conduct. The aim of the present study was to evaluate the criterion and construct validity of the Japanese language version of the CSB (CSB-J) in Japanese patients with schizophrenia.

Methodology/Principal Findings: Forty Japanese patients with schizophrenia and 40 Japanese healthy controls with matching age, gender, and premorbid intelligence quotient were enrolled. The CSB-J and the Brief Assessment of Cognition in Schizophrenia, Japanese-language version (BACS-J) were performed once. The structure of the CSB-J was also evaluated by a factor analysis. Similar to the BACS-J, the CSB-J was sensitive to cognitive impairment in Japanese patients with schizophrenia. Furthermore, there was a significant positive correlation between the CSB-J composite score and the BACS-J composite score. A factor analysis showed a three-factor model consisting of memory, speed, and social cognition factors.

Conclusions/Significance: This study suggests that the CSB-J is a useful and rapid automatically administered computerized battery for assessing broad cognitive domains in Japanese patients with schizophrenia.

Competing Interests: The authors have the following competing interests: Drs. Darby and Maruff are employees of CogState Ltd which developed Cogstate Schizophrenia Battery. There are no patents, products in development or marketed products to declare. This does not alter our adherence to all the PLoS ONE policies on sharing data and materials, as detailed online in the guide for authors. Dr. Kenji Hashimoto is a member of editorial Board of PLOS ONE. All other authors have declared that no competing interests exist.

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Introduction

Cognitive impairment, a core symptom of schizophrenia, is present at illness onset and usually persists even when psychotic symptoms have been successfully treated [1,2]. Furthermore, cognitive impairment is highly related to functional outcome in patients with schizophrenia [3,4]. Therefore, treatment of cognitive impairment is currently an important focus for psychopharmacology [5–10].

In contrast, the lack of an accepted standard battery for measuring cognitive impairment in patients with schizophrenia

had been a major obstacle to regulatory approval of cognition-enhancing treatments. Currently, National Institute of Mental Health - Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative - Consensus Cognitive Battery (MCCB) is available for the measurement of cognitive changes in patients with schizophrenia [11,12]. The MCCB has seven domains of cognitive function, including verbal learning, speed of processing, attention/vigilance, working memory, visual learning, reasoning and problem solving, and social cognition [11]. The MCCB was approved by Food and Drug

Administration for use in clinical trials for cognitive improvement in schizophrenia [13]. However, a Japanese version of the MCCB is not yet available. In contrast, the Japanese language version of the Brief Assessment of Cognition in Schizophrenia (BACS) [14,15] has been used to measure cognitive impairments in Japanese patients with schizophrenia.

Like the BACS, the CogState Schizophrenia Battery (CSB) has been developed to provide a briefer standardized assessment of cognition in schizophrenia. Although the BACS includes only four of the seven cognitive domains of the MATRICS initiative [16,17], the CSB includes all the seven cognitive domains [18,19]. Formal validation studies have shown the CSB to have very good sensitivity to cognitive impairment in patients with chronic schizophrenia, and require approximately 40 min for administration [18,19]. There is also a strong correlation between the composite scores from the CSB and the MCCB measures in patients with schizophrenia. Furthermore, both composite scores also correlate strongly with scores on Performance-Based Skills Assessment [19]. Importantly, because the CSB was developed specifically for the measurement of cognitive change the component tasks show minimal practice effects with repeated assessment, even during very brief re-test intervals [19].

The aim of the current study is to assess the validity of the Japanese language version of the CSB (CSB-J) in Japanese patients with schizophrenia by comparing performance on this battery to that of the Japanese language version of the BACS (BACS-J) already validated for use in Japan.

Methods

Subjects

Forty patients with schizophrenia were recruited at Chiba University Hospital (Chiba, Japan), The University of Tokyo Hospital (Tokyo, Japan), National Center Hospital, National Center of Neurology and Psychiatry (Tokyo, Japan), Toyama University Hospital (Toyama, Japan), and Tokushima University Hospital (Tokushima, Japan). All patients met the DSM-IV criteria for schizophrenia. No patient had received electroconvulsive therapy. There were no specific medication criteria for inclusion in the patient group. Twenty-five of 40 patients were treated with a single second-generation antipsychotic medication (risperidone, n = 8; aripiprazole, n = 7; olanzapine, n = 6; perospirone, n = 3; quetiapine, n = 1), four patients were treated with a single first-generation antipsychotic (haloperidol, n = 1; fluphenazine, n = 1; bromperidol, n = 1; sulpiride, n = 1), nine patients were treated with a combination of antipsychotic drugs (aripiprazole and quetiapine, n = 2; risperidone and quetiapine, n = 1; risperidone and haloperidol, n = 1; risperidone and levomepromazine, n = 1; haloperidol and levomepromazine, n = 1; haloperidol and zotepine, n = 1; risperidone, haloperidol, and bromperidol, n = 1; risperidone, haloperidol, and zotepine, n = 1), and two patients were medication free. Only two female patients were inpatients.

Forty healthy controls were recruited at the same five sites. They were screened with the Structured Clinical Interview for DSM-IV Axis I Disorders, Non-Patient Edition and were required not to have an Axis I disorder according to DSM-IV criteria. None had a first-degree family history of schizophrenia or schizoaffective disorder.

Inclusion criteria for all subjects in both groups included proficiency in Japanese language, normal or corrected-to-normal visual function, and at least a 9th-grade education. Exclusion criteria for all subjects in both groups included any current or past histories of neurological disorders (other than schizophrenia for the

patient group), including head injury, cerebral vascular disorders, epilepsy, or alcohol or drug use disorders. No subject was treated with donepezil. Participants who had severe symptoms of depression (defined by the Japanese version of the Calgary Depression Scale for Schizophrenia (JCDSS) [20,21] score of more than 9) were excluded from the study. Smokers were excluded because nicotine and nicotine withdrawal might have effects on cognition.

Study investigators made a concerted effort to recruit healthy controls who would match the patients on age, male/female ratio, and premorbid intelligence quotient (IQ) as assessed by the Japanese Adult Reading Scale-25 words version (JART-25) [22], which is Japanese version of National Adult Reading Test. Age was considered the primary demographic variable of interest since it was likely to have the greatest impact on cognition. The 40 subjects of both groups were divided into 4 age groups (1, 20–29 years old; 2, 30–39 years old; 3, 40–49 years old; 4, 50–65 years old). Prior to commencement of the study, all subjects provided written informed consent after receiving a full explanation regarding the nature of the study and potential risks and benefits of study participation. The study was approved by the relevant ethics committee of each institute and performed in accordance with the Declaration of Helsinki II. The ethics committees of each institute were: the Ethics Committee of Chiba University Graduate School of Medicine (Chiba, Japan), the Ethical Committee of the Faculty of Medicine, University of Tokyo (Tokyo, Japan), the Ethics Committee of National Center of Neurology and Psychiatry (Tokyo, Japan), the Committee on Medical Ethics of Toyama Medical and Pharmaceutical University (Toyama, Japan), and the Ethics Committee of University of Tokushima (Tokushima, Japan).

Assessment procedures

All subjects completed two batteries of cognitive tests administered by trained psychiatrists or psychologists. All subjects received the CSB-J followed by the BACS-J version A. JART-25 was completed after the BACS-J. All subjects were tested in a single day. In addition, the Positive and Negative Syndrome Scale (PANSS) [23] was completed along with the BACS-J. Short breaks of five minutes or less were provided as needed throughout testing. Subjects were instructed to avoid caffeine in all forms from 20 minutes prior to assessments to the end of all tests.

The CSB-J consists of eight tasks that measure verbal learning (International Shopping List Task; ISLT), speed of processing (Detection Task; DET), attention/vigilance (Identification Task; IDN), visual working memory (One Back Task; ONB), visual memory (One Card Learning Task; OCL), spatial working memory (Continuous Paired Association Learning Task; CPAL), reasoning and problem solving (Groton Maze Learning Task; GML), and social cognition (Social Emotional Cognition Task; SECT). The primary measure from each task of the CSB-J was standardized by creating Z-scores whereby healthy control mean was set to zero and the standard deviation set to one, following the methodological procedure used by Keefe et al. [14]. A composite score was calculated by averaging all Z-scores of the eight primary measures from the CSB-J. In this study, we used the original version of the CSB with a slight modification. First, the Two Back Task was omitted to reduce test duration because we considered the ONB sufficient to assess working memory function [19]. Second, the CPAL can provide another non-verbal paired associate learning [24]. Third, the list of words in the ISLT was customized for the study as recommended by the authors to match regional Japanese culture and minimize cross-cultural test bias [25]. Fourth, stimuli in the SECT were also customized to only

include faces with a Mongoloid countenance to avoid any other-race effects that can occur on tasks that use representations of human faces [26].

The CSB-J data were uploaded to a secure account on the CogState server (http://www.cogstate.com). Uploaded outcome parameters were calculated using custom software blind to diagnosis. Logarithmic and arcsine transformations for speed and accuracy measures respectively were performed in order to avoid violation of necessary statistical preconditions. A description of the battery's administration and the eight cognitive tasks has been reported previously for non-Japanese subjects [19,27].

Data analysis

Student's t-test and Fisher's exact test were used to examine differences between groups. For the analysis of concurrent validity, Pearson product-moment correlations were computed between scores on subtests of the CSB-J and the BACS-J within each cognitive domain. Stepwise General Linear Models (GLM) with the CSB-J composite score or subscores as the dependent variable were conducted. At first, with combined patients' and controls' data, GLM were used to evaluate the effects of the following independent variables on cognitive performance: age, sex, premorbid IQ, education, JCDSS score. Second, with patients' data, GLM were used to evaluate the effects of the following independent variables on cognitive performance: age, gender, premorbid IQ, illness duration, duration of untreated psychosis (DUP), the dosage of antipsychotic medication, the dosage of anticholinergic medication, PANSS positive syndrome scale score, PANSS negative syndrome scale score, PANSS general psychopathology scale score. The structure of the CSB-J was determined by performing the Maximum Likelihood extraction methods with oblique rotation. The Kruskal-Wallis test was used to compare cognitive impairment among different subtypes of schizophrenia. Values of $p<0.05$ were considered to indicate statistical significance.

Results

Demographic data and clinical variables

Demographic and clinical variables are presented in Table 1. Age, gender, estimated premorbid IQ and education did not differ for the two groups. The JCDSS score in patients was significantly higher than that of healthy controls, indicating that the schizophrenia patients group suffered more depressive symptoms.

Missing data across all sessions and administration time

The total amount of missing data across all tasks within the CSB-J was 1.25%. The reason for missing data was the time restriction of each subtest of the CSB-J. There was no missing data for the BACS-J subtests. The total administration time of the CSB-J (51.1±12.2 min (mean ± SD)) was significantly (t = 10.719, $p<0.001$) longer than that of the BACS-J (35.6±4.4 min (mean ± SD)).

Validity and stepwise analysis

Figure 1 and 2 shows the performance of patients on each of the primary measures and composite score of the CSB-J and the BACS-J compared to the healthy control, respectively. Significant differences in scores between the patients and the controls were observed for all of the subtests of the CSB-J and the BACS-J.

The CSB-J composite score was significantly correlated with the BACS-J composite score ($r=0.709$; $p<0.001$ for patients, $r=0.483$; $p<0.01$ for controls; $r=0.760$; $p<0.001$ for total subjects) as shown in Table 2 and Figure 3. Stepwise GLM

showed that age and premorbid IQ were independent predictors of the CSB-J composite scores. Lower cognitive performance was associated with increased age and lower premorbid IQ. After accounting for age and premorbid IQ, the difference between both composite scores remained. Other clinical variables were not correlated with the CSB-J composite score.

Next, we examined correlations between corresponding subtests from the CSB-J and the BACS-J. Because the BACS-J includes only four of the seven cognitive domains selected by the MATRICS initiative, we examined correlations of corresponding subtests in only these four domains. ISLT score and DET score were significantly correlated with the BACS-J verbal memory score ($r=0.725$, $p<0.001$) and the BACS-J symbol coding score ($r=0.466$, $p<0.01$) in patients, respectively. There were no significant correlations between other corresponding subtests (Table 2).

Furthermore, we examined the effect of five subtypes of schizophrenia on the CSB-J scores in patients with schizophrenia although the number of each subtype was small. The CSB-J score in each subtype is shown in Table S1. The disorganized subtype (n = 3) demonstrated intact cognition. The paranoid subtype (n = 20) and the catatonic subtype (n = 4) performed significantly worse on ISLT and the CSB-J composite score than controls. The undifferentiated subtype (n = 4) performed significantly worse on ISLT, IDN, and composite score than controls. The residual subtype (n = 9) performed significantly worse on broader domains than controls, and had stronger impairment on the CSB-J composite score (Figure 4 and Table S1).

Factor analysis of the CSB-J subtests

In a factor analysis of the CSB-J, the eigenvalue-greater-than-one rule and scree plot converged on a three-factor solution that accounted for 53.8% of the total variance. The Kaiser-Mayer-Olkin measure was calculated at 0.587 and Bartlett's test of sphericity was significant at $p<0.001$. The factor loadings are presented in Table 3. Subtests that needed memory loaded on Factor 1, including CPAL, OCL, ISLT, and GML. Subtests that needed speed loaded on Factor 2, including DET and IDN. The SECT loaded on Factor 3. The ONB was not associated with this three-factor solution.

Discussion

The present study is the first one to report the use of a complete MCCB compatible battery in Japanese schizophrenia patients and shows that the CSB-J is a useful neuropsychological battery for assessing global cognitive impairment in Japanese patients with schizophrenia. The CSB-J was easy to use and well tolerated by patients with a 98.8% completion rate and acceptable administration time with mean of 51.1 minutes. Although the administration time of the CSB-J was about 15 minutes longer than that of the partial MCCB BACS-J battery (with average of 35.6 minutes administration duration), the difference was probably in part because the CSB-J covered more cognitive domains than the BACS-J. In addition, there was a significant correlation between the CSB-J and the BACS-J composite scores in both the patients with schizophrenia and healthy control subjects groups, consistent with the previous results using the original English version of the CSB and standardized tests and the MCCB [18,19].

The results of this study also provide evidence of good construct validity for verbal memory and attentional domains between the CSB-J and BACS-J tasks, which are considered to evaluate these abilities. In particular, the ISLT and DET scores of the CSB-J were significantly correlated with the verbal memory and the

Table 1. Demographic and symptom information.

	Controls (n = 40)	Patients (n = 40)	p-value
Age (years)	39.6±11.9 (22–59)	39.6±12.3 (22–65)	1.000
Male/Female	20/20	20/20	1.000
Premorbid IQ	107.1±8.5 (89–120)	103.7±10.1 (79–120)	0.114
Education (years)	15.0±1.8 (12–20)	14.3±2.0 (10–20)	0.139
JCDSS	0.6±1.4 (0–6)	2.2±2.4 (0–9)	0.001
Illness duration (years)		15.6±11.6 (2–38)	
Duration of untreated psychosis (years)		2.5±6.0 (0–37)	
Chlorpromazine equivalents (mg)		410.8±305.6 (0–1250)	
Biperiden equivalents (mg)		1.0±1.9 (0–6)	
PANSS positive		14.1±5.2 (6–24)	
PANSS negative		17.9±6.1 (9–36)	
PANSS general		33.1±10.9 (18–47)	

Data are the mean ± S.D. Parenthesis is the range.
JCDSS: the Japanese version of Calgary Depression Scale for Schizophrenia.
PANSS: Positive and Negative Syndrome Scale.
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symbol coding scores of the BACS-J in patients, respectively. However, there were no significant correlations between the other subscores of the CSB-J and the corresponding subscores of the BACS-J that are considered to evaluate speed of processing, working memory, and reasoning or problem solving. These differences presumably relate to different task requirements. For example, the BACS-J token motor test requires an ability to coordinate both hands simultaneously, whilst the CSB-J IDN task requires simpler motor abilities for pushing the response buttons. Prior good correlations for the IDN task and information processing speed measures have been reported in non-Japanese schizophrenic patients [18], and a poor correlation between the token motor test and a corresponding conventional test [14,28], suggest that these tests measure differing abilities. Likewise, verbal fluency is associated with multiple cognitive abilities, including speed of processing, reasoning ability and other aspects of executive function such as inhibition [29]. Similarly, the tasks

evaluating working memory from the different batteries had significant differences. The ONB and CPAL tasks using the CSB-J probably correlate with visual and spatial working memory, whilst the digit sequencing of the BACS-J may correlate less with visual and more with verbal working memory. With respect to reasoning and problem solving, although both the GML task of the CSB-J and the Tower of London from the BACS-J require planning, inhibition, and working memory, the latter has been considered more of a planning task [30], whereas the GML task appears to highlight spatial working memory abilities [31]. Differences between the constructs evaluated by these two batteries appear a more salient explanation for the lack of correlations, since both the CSB-J subtests and the BACS-J subtests have been reported to be significantly correlated with the corresponding standard battery subscores [15,19].

The factor analysis performed on the CSB-J suggests that three factors of cognitive performance can be derived from the CSB-J scores. The first factor had memory as a common ability and included the CPAL, OCL, ISLT, and GML tasks. A second speed
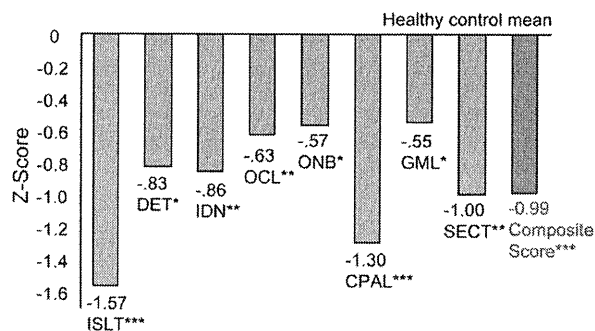

Figure 1. Magnitude of impairment relative to matched healthy controls on each cognitive measure from the CSB-J. Abbreviation: ISLT International Shopping List Task, DET Detection Task, IDN Identification Task, OCL One Card Learning Task, ONB One Back Task, CPAL Continuous Paired Association Task, GML Groton Maze Learning Task. Numbers of the figure are Z-score. *p<0.05, **p<0.01, ***p<0.001.
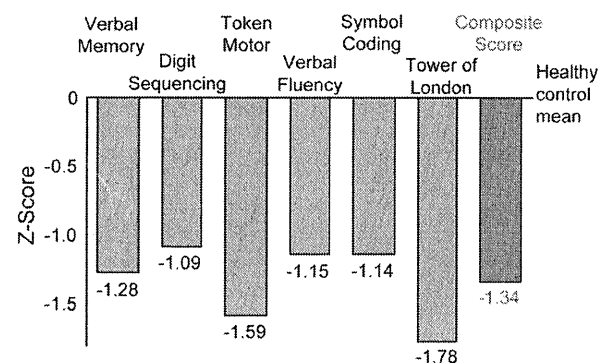doi:10.1371/journal.pone.0020469.g001

Figure 2. Magnitude of impairment relative to matched healthy controls on each cognitive measure from the BACS-J. Numbers of the figure are Z-score. All subtests and composite score were p<0.001.
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