

rs16944 [16-18]. However, this association was not confirmed in other studies [19,20]. Furthermore, none of the previous studies in Asian populations have obtained evidence for an association between *IL-1 $\beta$*  gene and schizophrenia [21-23]. All of the aforementioned association studies, except for that of Shirts, et al. [19], examined only rs16944 and/or rs1143634. Therefore, the role of other *IL-1 $\beta$*  gene polymorphisms remains to be determined. We here examined 5 tagging polymorphisms of the *IL-1 $\beta$*  gene for an association with schizophrenia in a Japanese sample.

## Methods

### Subjects

Subjects were 533 patients with schizophrenia (302 males: mean age  $\pm$  standard deviation  $43.4 \pm 13.0$  years; 233 females; mean age  $44.8 \pm 15.3$  years) and 1136 healthy controls (388 males: mean age  $44.6 \pm 17.3$  years; 748 females;  $46.3 \pm 15.6$  years). The mean age at onset was  $23.9 \pm 8.0$  and  $25.8 \pm 9.8$  years for male and female patients, respectively. All subjects were biologically unrelated Japanese individuals, based on their self-reports, and were recruited from the outpatient clinic of the National Center of Neurology and Psychiatry Hospital, Tokyo, Japan or through advertisements in free local information magazines and by our website announcement. Consensus diagnosis by at least two psychiatrists was made for each patient according to the Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition criteria [24], on the basis of unstructured interviews and information from medical records. The controls were healthy volunteers with no current or past history of psychiatric treatment, and were screened using the Japanese version of the Mini International Neuropsychiatric Interview (M.I.N.I.) [25,26] by a research psychiatrist to rule out any axis I psychiatric disorders. Participants were excluded if they had prior medical histories of central nervous system disease or severe head injury, or if they met the criteria for substance abuse or dependence, or mental retardation. The study protocol was approved by the ethics committee at the National Center of Neurology and Psychiatry, Japan. After description of the study, written informed consent was obtained from every subject. Most of the subjects had participated in our previous genetic association studies [27,28]. Some of the control subjects had also participated in our previous studies which examined *IL-1 $\beta$*  gene polymorphisms [29,30].

### Genotyping

Five tagging single nucleotide polymorphisms (SNPs) (rs2853550, rs1143634, rs1143633, rs1143630, rs16944) in a region 1 kilobase (kb) upstream to 1 kb downstream of the *IL-1 $\beta$*  gene (chromosome 2: 113,302,808 - 113,311,827 bp) were selected by Haploview 4.2 [31]

using Japanese and Chinese population in the HapMap SNP set (version 22), at an  $r^2$  threshold of 0.80 with a minor allele frequency greater than 0.1. Genomic DNA was prepared from the venous blood according to standard procedures. The SNPs were genotyped using the TaqMan 5'-exonuclease allelic discrimination assay. Thermal cycling conditions for polymerase chain reaction were 1 cycle at 95°C for 10 minutes followed by 50 cycles of 92°C for 15 seconds and 60°C for 1 minute. The allele-specific fluorescence was measured with ABI PRISM 7900 Sequence Detection Systems (Applied Biosystems, Foster city, CA, USA). Genotype data were read blind to the case-control status. Ambiguous genotype data were not included in the analysis. The call rates for each SNP ranged from 97.7% to 98.6%. The genotyping failure rate for all SNPs combined was < 2%. In 92 subjects, all 5 SNPs were genotyped in duplicate to ensure genotyping accuracy, and the concordance rate of called genotypes was over 99%.

### Statistical analysis

Deviations of genotype distributions from the Hardy-Weinberg equilibrium (HWE) were assessed with the exact test described by Wigginton et al [32]. Genotype and allele distributions were compared between patients and controls by using the  $\chi^2$  test for independence or with Fisher's exact test. The above statistical analyses were performed using PLINK version 1.07 [33].

Haploview 4.2 [31] was used to estimate haplotype frequencies and linkage disequilibrium (LD) coefficients. Haplotypes with frequencies > 1% were included in the association analysis. Permutation procedure (10,000 replications) was used to determine the empirical significance.

Statistical tests were two tailed and statistical significance was considered when  $P < 0.05$ . Significance level corrected for multiple comparisons of 5 SNPs was set at  $P < 0.013$  by a method proposed by Li et al [34], which was calculated using SNPSpD (SNP Spectral Decomposition) software [35].

Power calculations were performed using the Power Calculator for Two Stage Association Studies (<http://www.sph.umich.edu/csg/abecasis/CaTS/>). Power was calculated under prevalence of 0.01 using an allelic model with an alpha level of 0.05. Assuming disease allele frequencies of 0.20 and 0.40, our sample had 80% statistical power to detect relative risks of 1.28 and 1.23, respectively. Similarly, we had 90% power to detect relative risks of 1.33 and 1.27.

Since several aspects of immunity have marked sex differences [36], analyses were performed not only for the entire sample but also for each gender separately. Assuming allele frequency of 0.40, male and female samples each had 80% statistical power to detect relative risks of 1.35 and 1.34, respectively.

**Table 1 Association analysis of the 5 SNPs in both genders combined**

SNP name	Allele 1/2		N	Males							HWE P-value
				Genotype			Allele		P-value		
				1/1	1/2	2/2	1	2	Genotype	Allele	
rs2853550	A/G	Schizophrenia	531	9 (0.02)	128 (0.24)	394 (0.74)	146 (0.14)	916 (0.86)	0.23	0.088	0.86
		Controls	1115	14 (0.01)	232 (0.21)	869 (0.78)	260 (0.12)	1970 (0.88)			
rs1143634	A/G	Schizophrenia	525	1 (0.00)	41 (0.08)	483 (0.92)	43 (0.04)	1007 (0.96)	0.97 <sup>(a)</sup>	0.90	0.59
		Controls	1121	2 (0.00)	90 (0.08)	1029 (0.92)	94 (0.04)	2148 (0.96)			
rs1143633	C/T	Schizophrenia	524	111 (0.21)	249 (0.48)	164 (0.31)	471 (0.45)	577 (0.55)	0.035	0.0089	0.38
		Controls	1123	188 (0.17)	525 (0.47)	410 (0.37)	901 (0.40)	1345 (0.60)			
rs1143630	T/G	Schizophrenia	520	13 (0.03)	140 (0.27)	367 (0.71)	166 (0.16)	874 (0.84)	0.88	0.66	1.00
		Controls	1119	24 (0.02)	296 (0.26)	799 (0.71)	344 (0.15)	1894 (0.85)			
rs16944	A/G	Schizophrenia	521	123 (0.24)	253 (0.49)	145 (0.28)	499 (0.48)	543 (0.52)	0.18	0.060	0.54
		Controls	1111	226 (0.20)	534 (0.48)	351 (0.32)	986 (0.44)	1236 (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.

## Results

Genotype and allele distributions of the examined SNPs for the entire sample, males, and females are shown in Table 1, 2, and 3, respectively. The genotype distributions did not significantly deviate from the HWE in any of the SNPs examined. Significant differences in genotype and allele distributions were found between the patients with schizophrenia and controls for rs1143633. The C allele was significantly more common in patients than in controls (odds ratio 1.22, 95% confidence interval (CI) 1.05 to 1.41,  $P = 0.0089$ ). This association remained significant after correcting for multiple testing of 5 SNPs (corrected  $P = 0.013$ ). When the analysis was performed separately in each gender, significant difference between patients and controls in allele distribution of rs1143633 was observed only in females (odds ratio 1.34, 95% CI 1.08 to 1.66,  $P = 0.0073$ ). The A allele of rs16944 also showed a trend towards association with schizophrenia in female subjects (odds ratio 1.26, 95% CI 1.02 to 1.56,  $P = 0.032$ ).

Linkage disequilibrium (LD) coefficients ( $D'$  and  $r^2$ ) and haplotype blocks are shown in Figure 1. Results of the haplotype association analyses are shown in Table 4. No significant difference in haplotype distribution was found between patients with schizophrenia and controls (all  $P > 0.05$  by permutation test).

## Discussion

To our knowledge, the present study is the largest study to date that examined the *IL-1β* gene polymorphisms for association with schizophrenia. The results provide the first evidence suggesting that the C allele of rs1143633 is associated with schizophrenia.

The study in a United States population by Shirts et al [19] was the only one that previously examined the association of schizophrenia with rs1143633, in which no significant difference was found in allele frequencies between patients and controls. Although Watanabe et al [23] have also examined 9 SNPs of the IL-1 gene complex in Japanese subjects, none of the SNPs examined in their study was in remarkable linkage disequilibrium with rs1143633 or rs16944 (all  $r^2 < 0.1$  based on HapMap Japanese and Han Chinese population data, release 22). The inconsistent results regarding the effect of rs1143633 between Shirts, et al [19] and our study may be attributable to ethnic difference. Indeed, a recent meta-analysis has shown a significant association of the G allele of rs16944 and the G allele carrier status of rs1143634 with a risk of schizophrenia in Caucasian, but not in Asian, populations [37]. Our samples provided sufficient power to detect relatively small relative risks, and therefore suggest that rs16944 and rs1143634 have no major effect on

**Table 2 Association analysis of the 5 SNPs in males**

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

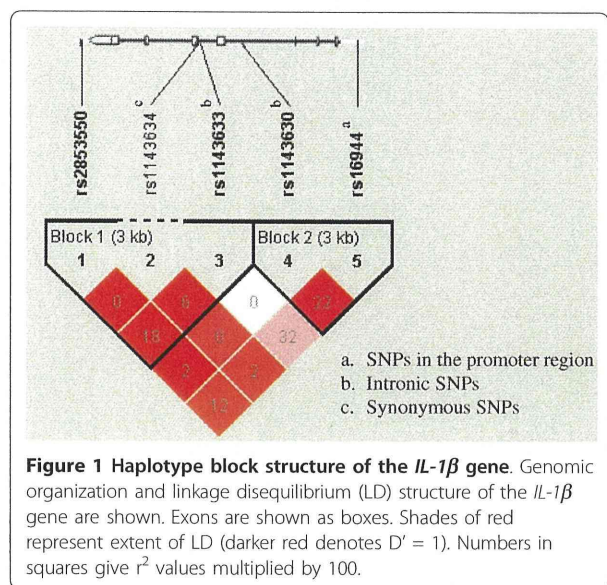
**Table 3 Association analysis of the 5 SNPs in females**

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



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	$\chi^2$	Nominal P value	Permutation P value	Carrier	Non-carrier	$\chi^2$	Nominal P value	Permutation P value
1	GT	Schizophrenia	336.3 (0.559)	265.7 (0.441)	0.557	0.456	0.957	251.0 (0.541)	213.0 (0.459)	6.240	0.0125	0.118
		Controls	447.9 (0.579)	326.1 (0.421)				901.0 (0.606)	585.0 (0.394)			
	GC	Schizophrenia	183.1 (0.304)	418.9 (0.696)	0.216	0.642	0.995	149.0 (0.321)	315.0 (0.679)	2.298	0.130	0.691
		Controls	226.4 (0.293)	547.6 (0.707)				422.5 (0.284)	1063.5 (0.716)			
	AC	Schizophrenia	82.6 (0.137)	519.4 (0.863)	0.215	0.643	0.995	63.7 (0.137)	400.3 (0.863)	3.281	0.0701	0.461
		Controls	99.6 (0.129)	674.4 (0.871)				158.5 (0.107)	1327.5 (0.893)			
GG	Schizophrenia	321.4 (0.534)	280.6 (0.466)	0.154	0.694	0.996	231.2 (0.503)	228.8 (0.497)	5.012	0.0252	0.207	
	Controls	422.6 (0.545)	353.4 (0.455)				837.4 (0.562)	652.6 (0.438)				
2	GA	Schizophrenia	183.5 (0.305)	418.5 (0.695)	0.040	0.841	1.00	156.4 (0.340)	303.6 (0.660)	5.326	0.0210	0.178
		Controls	232.7 (0.300)	543.3 (0.700)				422.8 (0.284)	1067.2 (0.716)			
	TA	Schizophrenia	97.1 (0.161)	504.9 (0.839)	0.081	0.776	0.999	72.4 (0.157)	387.6 (0.843)	0.027	0.869	1.00
		Controls	120.7 (0.156)	655.3 (0.844)				229.8 (0.154)	1260.2 (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-1 $\beta$  has been observed in schizophrenic patients [9]. The changes in mRNA levels may reflect the genetic variation in *IL-1 $\beta$*  gene. The findings on biological roles of *IL-1 $\beta$*  polymorphisms, however, have not been consistent across studies. A/A genotype of rs16944 has been associated with higher gastric mucosa IL-1 $\beta$  levels in *H. pylori* positive population [48]. On the other hand, subjects with G/G genotype showed an increased release of IL-1 $\beta$  from mononuclear cells after stimulation with lipopolysaccharide [49]. Recent studies suggest that the functional role of rs16944 may depend on the *IL-1 $\beta$*  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-1 $\beta$ . On the other hand, the influence of rs1143633 on IL-1 $\beta$  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-1 $\beta$*  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-1 $\beta$*  gene variation in females. To our knowledge, no previous studies have examined the gender differences in the association between *IL-1 $\beta$*  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- $\kappa$ B, which is activated by IL-1 $\beta$ . Taken together with our results, the influence of IL-1 $\beta$  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-1 $\beta$*  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-1 $\beta$*  gene is associated with schizophrenia susceptibility in a Japanese population and that the influence of *IL-1 $\beta$*  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-1 $\beta$  in the etiology of schizophrenia. Future studies are warranted to replicate the present findings and to reveal the functional role of *IL-1 $\beta$*  gene in pathophysiology of schizophrenia.

## Acknowledgements

This study was supported by Health and Labor Sciences Research Grants (Comprehensive Research on Disability, Health, and Welfare), Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (JSPS), Core Research of Evolutional Science & Technology (CREST), Japan Science and Technology Agency (JST), the Strategic Research Program for Brain Sciences by the Ministry of Education, Culture, Sports, Science and Technology of Japan (Understanding of molecular and environmental bases for brain health), and Intramural Research Grant for Neurological and Psychiatric Disorders of NCNP (H.K.).

## Author details

<sup>1</sup>Department of Mental Disorder Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Kodaira, Tokyo, 187-8502, Japan. <sup>2</sup>Department of Psychiatry, Shinshu University School of Medicine, Matsumoto, 390-8621, Japan. <sup>3</sup>Core Research of Evolutional Science & Technology (CREST), Japan Science and Technology Agency (JST), Tokyo, 102-0075, Japan. <sup>4</sup>Department of Medical Genetics, Majors of Medical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, 305-8577, Japan. <sup>5</sup>Yokohama Shinryo Clinic, Yokohama, 221-0835, Japan. <sup>6</sup>National Center of Neurology and Psychiatry, Kodaira, Tokyo, 187-8502, Japan.

#### 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.

Received: 27 April 2011 Accepted: 16 August 2011

Published: 16 August 2011

#### References

- Baker I, Masserano J, Wyatt RJ: Serum cytokine concentrations in patients with schizophrenia. *Schizophr Res* 1996, **20**:199-203.
- Barak V, Barak Y, Levine J, Nisman B, Roisman I: Changes in interleukin-1 beta and soluble interleukin-2 receptor levels in CSF and serum of schizophrenic patients. *J Basic Clin Physiol Pharmacol* 1995, **6**:61-69.
- Katila H, Hurme M, Wahlbeck K, Appelberg B, Rimon R: Plasma and cerebrospinal fluid interleukin-1 beta and interleukin-6 in hospitalized schizophrenic patients. *Neuropsychobiology* 1994, **30**:20-23.
- Kim YK, Kim L, Lee MS: Relationships between interleukins, neurotransmitters and psychopathology in drug-free male schizophrenics. *Schizophr Res* 2000, **44**:165-175.
- Kim YK, Lee MS, Suh KY: Decreased interleukin-2 production in Korean schizophrenic patients. *Biol Psychiatry* 1998, **43**:701-704.
- Xu HM, Wei J, Hemmings GP: Changes of plasma concentrations of interleukin-1 alpha and interleukin-6 with neuroleptic treatment for schizophrenia. *Br J Psychiatry* 1994, **164**:251-253.
- Soderlund J, Schroder J, Nordin C, Samuelsson M, Walther-Jallow L, Karlsson H, Erhardt S, Engberg G: Activation of brain interleukin-1beta in schizophrenia. *Mol Psychiatry* 2009, **14**:1069-1071.
- Kowalski J, Blada P, Kucia K, Madej A, Herman ZS: Neuroleptics normalize increased release of interleukin-1 beta and tumor necrosis factor-alpha from monocytes in schizophrenia. *Schizophr Res* 2001, **50**:169-175.
- Liu L, Jia F, Yuan G, Chen Z, Yao J, Li H, Fang C: Tyrosine hydroxylase, interleukin-1beta and tumor necrosis factor-alpha are overexpressed in peripheral blood mononuclear cells from schizophrenia patients as determined by semi-quantitative analysis. *Psychiatry Res* 2010, **176**:1-7.
- Gilmore JH, Fredrik Jarskog L, Vadlamudi S, Lauder JM: Prenatal infection and risk for schizophrenia: IL-1beta, IL-6, and TNFalpha inhibit cortical neuron dendrite development. *Neuropsychopharmacology* 2004, **29**:1221-1229.
- Marx CE, Jarskog LF, Lauder JM, Lieberman JA, Gilmore JH: Cytokine effects on cortical neuron MAP-2 immunoreactivity: implications for schizophrenia. *Biol Psychiatry* 2001, **50**:743-749.
- Levinson DF, Mahtani MM, Nancarrow DJ, Brown DM, Kruglyak L, Kirby A, Hayward NK, Crowe RR, Andreasen NC, Black DW, et al: Genome scan of schizophrenia. *Am J Psychiatry* 1998, **155**:741-750.
- DeLisi LE, Shaw SH, Crow TJ, Shields G, Smith AB, Larach WW, Wellman N, Loftus J, Nanthakumar B, Razi K, et al: A genome-wide scan for linkage to chromosomal regions in 382 sibling pairs with schizophrenia or schizoaffective disorder. *Am J Psychiatry* 2002, **159**:803-812.
- Lewis CM, Levinson DF, Wise LH, DeLisi LE, Straub RE, Hovatta I, Williams NM, Schwab SG, Pulver AE, Faraone SV, et al: Genome scan meta-analysis of schizophrenia and bipolar disorder, part II: Schizophrenia. *Am J Hum Genet* 2003, **73**:34-48.
- Faraone SV, Hwu HG, Liu CM, Chen WJ, Tsuang MM, Liu SK, Shieh MH, Hwang TJ, Ou-Yang WC, Chen CY, et al: Genome scan of Han Chinese schizophrenia families from Taiwan: confirmation of linkage to 10q22.3. *Am J Psychiatry* 2006, **163**:1760-1766.
- Hanninen K, Katila H, Saarela M, Rontu R, Mattila KM, Fan M, Hurme M, Lehtimäki T: Interleukin-1 beta gene polymorphism and its interactions with neuregulin-1 gene polymorphism are associated with schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 2008, **258**:10-15.
- Papiol S, Rosa A, Gutierrez B, Martin B, Salgado P, Catalan R, Arias B, Fananas L: Interleukin-1 cluster is associated with genetic risk for schizophrenia and bipolar disorder. *J Med Genet* 2004, **41**:219-223.
- Zanardini R, Bocchio-Chiavetto L, Scassellati C, Bonvicini C, Tura GB, Rossi G, Perez J, Gennarelli M: Association between IL-1beta -511C/T and IL-1RA (86bp)n repeats polymorphisms and schizophrenia. *J Psychiatr Res* 2003, **37**:457-462.
- Shirts BH, Wood J, Yolken RH, Nirnmaonkar VL: Association study of IL10, IL1beta, and IL1RN and schizophrenia using tag SNPs from a comprehensive database: suggestive association with rs16944 at IL1beta. *Schizophr Res* 2006, **88**:235-244.
- Betcheva ET, Mushiroda T, Takahashi A, Kubo M, Karachanak SK, Zaharieva IT, Vazharova RV, Dimova II, Milanova VK, Tolev T, et al: Case-control association study of 59 candidate genes reveals the DRD2 SNP rs6277 (C957T) as the only susceptibility factor for schizophrenia in the Bulgarian population. *J Hum Genet* 2009, **54**:98-107.
- Chowdari KV, Xu K, Zhang F, Ma C, Li T, Xie BY, Wood J, Trucco M, Tsoi WF, Saha N, et al: Immune related genetic polymorphisms and schizophrenia among the Chinese. *Hum Immunol* 2001, **62**:714-724.
- Tatsumi M, Sasaki T, Sakai T, Kamijima K, Fukuda R, Kunugi H, Hattori M, Nanko S: Genes for interleukin-2 receptor beta chain, interleukin-1 beta, and schizophrenia: no evidence for the association or linkage. *Am J Med Genet* 1997, **74**:338-341.
- Watanabe Y, Nunokawa A, Kaneko N, Muratake T, Koizumi M, Someya T: Lack of association between the interleukin-1 gene complex and schizophrenia in a Japanese population. *Psychiatry Clin Neurosci* 2007, **61**:364-369.
- American Psychiatric Association: *DSM-IV: Diagnostic and Statistical Manual of Mental Disorders*. 4 edition. Washington D.C.: American Psychiatric Press; 1994.
- Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC: The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998, **59**(Suppl 20):22-33, quiz 34-57.
- Otsubo T, Tanaka K, Koda R, Shinoda J, Sano N, Tanaka S, Aoyama H, Mimura M, Kamijima K: Reliability and validity of Japanese version of the Mini-International Neuropsychiatric Interview. *Psychiatry Clin Neurosci* 2005, **59**:517-526.
- Hashimoto R, Ohi K, Yasuda Y, Fukumoto M, Yamamori H, Takahashi H, Iwase M, Okochi T, Kazui H, Saitoh O, et al: Variants of the RELA gene are associated with schizophrenia and their startle responses. *Neuropsychopharmacology* 2011, **36**:1921-1931.
- Richards M, Iijima Y, Kondo H, Shizuno T, Hori H, Arima K, Saitoh O, Kunugi H: Association study of the vesicular monoamine transporter 1 (VMAT1) gene with schizophrenia in a Japanese population. *Behav Brain Funct* 2006, **2**:39.
- Sasayama D, Hori H, Teraishi T, Hattori K, Ota M, Matsuo J, Kawamoto Y, Kinoshita Y, Higuchi T, Amano N, Kunugi H: Association of interleukin-1beta genetic polymorphisms with cognitive performance in elderly females without dementia. *J Hum Genet* .
- Sasayama D, Hori H, Iijima Y, Teraishi T, Hattori K, Ota M, Fujii T, Higuchi T, Amano N, Kunugi H: Modulation of cortisol responses to the DEX/CRH test by polymorphisms of the interleukin-1beta gene in healthy adults. *Behav Brain Funct* 2011, **7**:23.
- Barrett JC, Fry B, Maller J, Daly MJ: Haploview: analysis and visualization of LD and haplotype maps. *Bioinformatics* 2005, **21**:263-265.
- Wigginton JE, Cutler DJ, Abecasis GR: A note on exact tests of Hardy-Weinberg equilibrium. *Am J Hum Genet* 2005, **76**:887-893.
- Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, Maller J, Sklar P, de Bakker PI, Daly MJ, Sham PC: PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet* 2007, **81**:559-575.
- Li J, Ji L: Adjusting multiple testing in multilocus analyses using the eigenvalues of a correlation matrix. *Heredity* 2005, **95**:221-227.
- Nyholt DR: A simple correction for multiple testing for single-nucleotide polymorphisms in linkage disequilibrium with each other. *Am J Hum Genet* 2004, **74**:765-769.
- Gillum TL, Kuennen MR, Schneider S, Moseley P: A review of sex differences in immune function after aerobic exercise. *Exerc Immunol Rev* 2011, **17**:104-121.
- Xu M, He L: Convergent evidence shows a positive association of interleukin-1 gene complex locus with susceptibility to schizophrenia in the Caucasian population. *Schizophr Res* 2010, **120**:131-142.



38. Stefansson H, Ophoff RA, Steinberg S, Andreassen OA, Cichon S, Rujescu D, Werge T, Pietilainen OP, Mors O, Mortensen PB, et al: **Common variants conferring risk of schizophrenia.** *Nature* 2009, **460**:744-747.
39. Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, Sklar P: **Common polygenic variation contributes to risk of schizophrenia and bipolar disorder.** *Nature* 2009, **460**:748-752.
40. Shi J, Levinson DF, Duan J, Sanders AR, Zheng Y, Pe'er I, Dudbridge F, Holmans PA, Whittemore AS, Mowry BJ, et al: **Common variants on chromosome 6p22.1 are associated with schizophrenia.** *Nature* 2009, **460**:753-757.
41. Ikeda M, Aleksic B, Kinoshita Y, Okochi T, Kawashima K, Kushima I, Ito Y, Nakamura Y, Kishi T, Okumura T, et al: **Genome-wide association study of schizophrenia in a Japanese population.** *Biol Psychiatry* 2011, **69**:472-478.
42. Yamada K, Iwayama Y, Hattori E, Iwamoto K, Toyota T, Ohnishi T, Ohba H, Maekawa M, Kato T, Yoshikawa T: **Genome-wide association study of schizophrenia in Japanese population.** *PLoS One* 2011, **6**:e20468.
43. Rietschel M, Mattheisen M, Degenhardt F, Kahn RS, Linszen DH, Os JV, Wiersma D, Bruggeman R, Cahn W, de Haan L, et al: **Association between genetic variation in a region on chromosome 11 and schizophrenia in large samples from Europe.** *Mol Psychiatry* .
44. McClay JL, Adkins DE, Aberg K, Bukszar J, Khachane AN, Keefe RS, Perkins DO, McEvoy JP, Stroup TS, Vann RE, et al: **Genome-wide pharmacogenomic study of neurocognition as an indicator of antipsychotic treatment response in schizophrenia.** *Neuropsychopharmacology* 2010, **36**:616-626.
45. Schwarz MJ, Chiang S, Muller N, Ackenheil M: **T-helper-1 and T-helper-2 responses in psychiatric disorders.** *Brain Behav Immun* 2001, **15**:340-370.
46. Schwarz MJ, Muller N, Riedel M, Ackenheil M: **The Th2-hypothesis of schizophrenia: a strategy to identify a subgroup of schizophrenia caused by immune mechanisms.** *Med Hypotheses* 2001, **56**:483-486.
47. Muller N, Riedel M, Gruber R, Ackenheil M, Schwarz MJ: **The immune system and schizophrenia. An integrative view.** *Ann N Y Acad Sci* 2000, **917**:456-467.
48. Hwang IR, Kodama T, Kikuchi S, Sakai K, Peterson LE, Graham DY, Yamaoka Y: **Effect of interleukin 1 polymorphisms on gastric mucosal interleukin 1beta production in Helicobacter pylori infection.** *Gastroenterology* 2002, **123**:1793-1803.
49. Iacoviello L, Di Castelnuovo A, Gattone M, Pezzini A, Assanelli D, Lorenzet R, Del Zotto E, Colombo M, Napoleone E, Amore C, et al: **Polymorphisms of the interleukin-1beta gene affect the risk of myocardial infarction and ischemic stroke at young age and the response of mononuclear cells to stimulation in vitro.** *Arterioscler Thromb Vasc Biol* 2005, **25**:222-227.
50. Chen H, Wilkins LM, Aziz N, Cannings C, Wyllie DH, Bingle C, Rogus J, Beck JD, Offenbacher S, Cork MJ, et al: **Single nucleotide polymorphisms in the human interleukin-1B gene affect transcription according to haplotype context.** *Hum Mol Genet* 2006, **15**:519-529.
51. Wen AQ, Wang J, Feng K, Zhu PF, Wang ZG, Jiang JX: **Effects of haplotypes in the interleukin 1beta promoter on lipopolysaccharide-induced interleukin 1beta expression.** *Shock* 2006, **26**:25-30.
52. Wen AQ, Gu W, Wang J, Feng K, Qin L, Ying C, Zhu PF, Wang ZG, Jiang JX: **Clinical relevance of interleukin-1beta promoter polymorphisms (-1470, -511 and -31) in patients with major trauma.** *Shock* 2009.
53. Hall SK, Perregaux DG, Gabel CA, Woodworth T, Durham LK, Huizinga TW, Breedveld FC, Seymour AB: **Correlation of polymorphic variation in the promoter region of the interleukin-1 beta gene with secretion of interleukin-1 beta protein.** *Arthritis Rheum* 2004, **50**:1976-1983.
54. Sharma RP, Pandey GN, Janicak PG, Peterson J, Comaty JE, Davis JM: **The effect of diagnosis and age on the DST: a metaanalytic approach.** *Biol Psychiatry* 1988, **24**:555-568.
55. Hori H, Teraishi T, Ozeki Y, Hattori K, Sasayama D, Matsuo J, Kawamoto Y, Kinoshita Y, Higuchi T, Kunugi H: **Schizotypal Personality in Healthy Adults Is Related to Blunted Cortisol Responses to the Combined Dexamethasone/Corticotropin-Releasing Hormone Test.** *Neuropsychobiology* 2011, **63**:232-241.
56. Ismail K, Murray RM, Wheeler MJ, O'Keane V: **The dexamethasone suppression test in schizophrenia.** *Psychol Med* 1998, **28**:311-317.
57. Lynch EA, Dinarello CA, Cannon JG: **Gender differences in IL-1 alpha, IL-1 beta, and IL-1 receptor antagonist secretion from mononuclear cells and urinary excretion.** *J Immunol* 1994, **153**:300-306.
58. Giron-Gonzalez JA, Moral FJ, Elvira J, Garcia-Gil D, Guerrero F, Gavilan I, Escobar L: **Consistent production of a higher TH1:TH2 cytokine ratio by**

stimulated T cells in men compared with women. *Eur J Endocrinol* 2000, **143**:31-36.

doi:10.1186/1744-9081-7-35

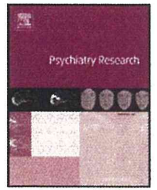
**Cite this article as:** Sasayama et al.: Possible association between *Interleukin-1beta* gene and schizophrenia in a Japanese population. *Behavioral and Brain Functions* 2011 **7**:35.

**Submit your next manuscript to BioMed Central and take full advantage of:**

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at  
www.biomedcentral.com/submit





## Relationships between season of birth, schizotypy, temperament, character and neurocognition in a non-clinical population

Hiroaki Hori\*, Toshiya Teraishi, Daimei Sasayama, Junko Matsuo, Yumiko Kawamoto, Yukiko Kinoshita, Hiroshi Kunugi

Department of Mental Disorder Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, 4-1-1, Ogawahigashi, Kodaira, Tokyo, 187-8502, Japan

### ARTICLE INFO

#### Article history:

Received 20 December 2010

Received in revised form 13 July 2011

Accepted 16 July 2011

#### Keywords:

Schizotypal personality

Schizophrenia

Season of birth

Cognitive function

Temperament

Character

### ABSTRACT

While schizophrenia has been associated with a slight excess of winter/early spring birth, it is unclear whether there is such an association in relation to schizotypal personality traits. Season of birth has also been reported to relate to temperament and character personality dimensions and cognitive functioning. Moreover, non-clinical schizotypy has been shown to be associated with mild cognitive impairment, although its precise nature is yet to be elucidated. Here we examined the relationships between season of birth, schizotypal traits, temperament and character, and cognitive function. Four hundred and fifty-one healthy adults completed the Schizotypal Personality Questionnaire (SPQ). The Temperament and Character Inventory (TCI) and a neuropsychological test battery consisting of full versions of the Wechsler Memory Scale-Revised and the Wechsler Adult Intelligence Scale-Revised, and the Wisconsin Card Sorting Test, were also administered to most of the participants. The total SPQ score of those born in winter was significantly higher than that of the remaining participants. Season of birth was not significantly associated with any of the TCI dimensions or cognitive test results. Significant but mild relationships between higher SPQ scores and lower scores on some aspects of IQ were observed. These results support the notion that schizotypy and schizophrenia are neurodevelopmental conditions on the same continuum.

© 2011 Elsevier Ireland Ltd. All rights reserved.

### 1. Introduction

Schizotypy refers to latent personality organization that indicates an individual's proneness to psychosis and, in particular, to schizophrenia (Raine et al., 1995). The dimensional model of schizotypal personality posits that the degree of schizotypal traits varies on a continuum where normality lies on one extreme, non-clinical to clinical schizotypy in the middle, and clinically expressed schizophrenia on the opposite extreme (Claridge, 1985, Kendler et al., 1991). In accord with this view, several lines of evidence have demonstrated a range of abnormalities in relation to schizotypal personality that are intrinsically similar to those seen in schizophrenia (Siever and Davis, 2004), such as neurophysiological (O'Driscoll et al., 1998; Kiang and Kutas, 2005), neurocognitive (Lenzenweger and Korfine, 1994; Gooding et al., 2006), neuroendocrinological (Mitropoulou et al., 2004; Hori et al., 2011) and neuroimaging (Folley and Park, 2005; Hori et al., 2008a) abnormalities.

On the other hand, little has been done to identify early-life origins that predict greater schizotypal traits in adulthood, although it is now well established that schizophrenia is to some extent associated with such origins. Among a variety of factors that originate early in life,

season of birth has been extensively studied in the epidemiology of schizophrenia, with most studies reporting a slight (approximately 10%) excess of winter/early spring birth in patients with schizophrenia (reviewed in Torrey et al., 1997; Davies et al., 2003). To better understand the etiology of and risk factors for schizophrenia in light of the dimensional model of this disorder, it would be of importance to investigate the possible effect of season of birth on schizotypal traits. To our knowledge, there have been four studies that shed light on this topic. Reid and Zborowski (2006), using a sample of undergraduate students from the Northeast United States, found significantly higher scores on the Perceptual-Aberration and Magical-Ideation scale, developed by Chapman and his colleagues, in individuals born in spring than those born in the other seasons. Kirkpatrick et al. (2008) found in undergraduates from the middle-eastern United States that June/July birth was associated with a proxy measure for the deficit syndrome, which was defined by combining the Chapman's Social Anhedonia Scale and the Beck Depression Inventory. Lahti et al. (2009), using a large cohort consisting of approximately 5000 people born in Northern Finland in 1966, showed that winter/autumn birth, in addition to several other early-life characteristics, predicted augmented negative schizotypal traits (as assessed with the Chapman's Physical Anhedonia Scale) in women. More recently, Cohen and Najolia (2011) screened more than 25,000 university students from the southern United States and showed that season of birth of individuals who scored extremely high on the Schizotypal Personality

\* Corresponding author. Tel.: +81 42 341 2711; fax: +81 42 346 1744.

E-mail address: [hori@ncnp.go.jp](mailto:hori@ncnp.go.jp) (H. Hori).



Questionnaire (SPQ, Raine, 1991) did not differ from that of those whose scores were less than one standard deviation above the mean. Taken together, findings to date on the association between season of birth and schizotypal traits have not been consistent and thus await further investigations.

Season of birth has also been reported to be associated with other personality traits, including temperament/character dimensions (Chotai et al., 2001, 2002, 2009; Kamata et al., 2009). Studies including ours have shown that temperament and character of patients with schizophrenia are markedly different from those of healthy controls, such that these patients, compared to healthy controls, exhibit lower novelty seeking, self-directedness and cooperativeness and higher harm avoidance (Guillem et al., 2002; Hori et al., 2008b). In addition, temperament and character personality dimensions have been shown to correlate with schizotypal personality (Daneluzzo et al., 2005; Bora and Veznedaroglu, 2007).

There also exists evidence that certain aspects of cognitive function could be affected by season of birth (Martin et al., 2004; McGrath et al., 2006; Gobet and Chassy, 2008). Interestingly, some studies have found an association between superior cognitive performance and winter/spring birth (McGrath et al., 2006; Gobet and Chassy, 2008), which might be counterintuitive to the fact that neurocognitive impairments are a core feature of schizophrenia. Another line of research has looked at the relationships between personality traits and neurocognitive functioning. As for the association between schizotypy and neurocognition, a number of studies in psychometrically identified schizotypes have, albeit not entirely unequivocally, found this condition to be associated with compromised functioning in various cognitive domains, including sustained attention (Lenzenweger, 2001; Gooding et al., 2006), spatial working memory (Park and McTigue, 1997), and executive function as assessed with the Wisconsin Card Sorting Test (WCST, Lenzenweger and Korfine, 1994; Daneluzzo et al., 1998). Although the relationship between temperament/character and cognition is less well studied, several studies have examined this relation among various psychiatric conditions. For instance, Bergvall et al. (2003) reported that higher self-directedness and cooperativeness were significantly associated with less errors in an attentional set-shifting task in a sample consisting of incarcerated offenders, correctional officers and medical aides. Similarly, Smith et al. (2008) showed that self-directedness and cooperativeness were strongly positively correlated with working memory and crystallized intelligence in non-psychotic siblings.

In this context, the present study sought to explore the associations of season of birth with schizotypal personality traits, temperament/character dimensions and cognitive function. In addition, we also attempted to clarify the relationships between schizotypal traits, temperament/character and cognitive functioning.

## 2. Methods

### 2.1. Participants

Participants were 451 Japanese adults (age range: 19–73 years) who resided in the western part of Tokyo. They were recruited between 2006 and 2010 from the community through advertisements in free local magazines and our website announcement, and also from hospital staff and their associates through flyers and by word of mouth. At the first visit, participants were interviewed using the Japanese version of the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998; Otsubo et al., 2005) by a research psychiatrist, and only those who demonstrated no current Axis I psychiatric disorders were enrolled in the study. In addition, those individuals who demonstrated one or more of the following conditions in a non-structured interview performed by an experienced psychiatrist were excluded: past or current regular contact to psychiatric services, having a history of regular use of psychotropics or substance abuse/dependence, presenting other obvious self-reported signs of past primary psychotic and mood disorders, and having a prior medical history of central nervous system disease or severe head injury. The present experiments on our participants were conducted in accordance with the Declaration of Helsinki. After the nature of the study procedures had been fully explained, written informed consent was obtained from all participants. The study was approved by the ethics committee of the National Center of Neurology and Psychiatry, Japan.

### 2.2. Personality assessment

Personality was assessed with two self-report questionnaires, which were distributed to each participant at our laboratory. He/she was allowed to take as much time as needed to complete the questionnaires, then returned them to us by mail or by hand.

#### 2.2.1. Schizotypal Personality Questionnaire (SPQ)

The SPQ (Raine, 1991) is a 74-item validated self-report questionnaire with a “yes/no” response format that incorporates DSM-III-R (American Psychiatric Association, 1987) criteria for a diagnosis of schizotypal personality disorder (SPD). All items endorsed “yes” are scored 1 point. The questionnaire consists of nine subscales, which have been found to load onto three factors: cognitive-perceptual (comprising the “ideas of reference,” “odd beliefs/magical thinking,” “unusual perceptual experiences” and “suspiciousness/paranoid ideation” subscales), interpersonal (“social anxiety,” “no close friends,” “constricted affect,” and “suspiciousness/paranoid ideation”), and disorganized (“eccentric/odd behavior and appearance” and “odd speech”) factors (Raine et al., 1994). We employed the Japanese version of the SPQ (Fujiwara, 1993), reliability and validity of which had been demonstrated to be similar to those of the original version (Raine, 1991). All participants completed this questionnaire.

#### 2.2.2. Temperament and Character Inventory (TCI)

TCI (Cloninger et al., 1993) is a 240-item (including 14 items which are not analyzed) self-report questionnaire; each item requires a true/false answer. The term temperament refers to automatic emotional reactions to subjective experiences that may be genetically transmitted and therefore stable over time. Four dimensions of temperament are distinguished: novelty seeking, harm avoidance, reward dependence, and persistence. Novelty seeking, harm avoidance, and reward dependence were assumed to relate to dopaminergic, serotonergic, and noradrenergic neurotransmission, respectively (Cloninger, 1987). The term character refers to concepts pertaining to the individual, focusing on personal differences in intentions, decisions and values. Three dimensions of character are distinguished: self-directedness, cooperativeness, and self-transcendence. The reliability and validity of the original American version of the TCI have been established (Cloninger et al., 1993; Svrakic et al., 1993). The Japanese version of the TCI translated and validated by Kijima et al. (1996, 2000) was used in the present study. Of the total 451 participants, 443 (98.2%) completed the TCI.

### 2.3. Cognitive test battery

A neurocognitive test battery, comprising full versions of the Wechsler Memory Scale-Revised (WMS-R, Wechsler, 1987; Sugishita, 2001) and the Wechsler Adult Intelligence Scale-Revised (WAIS-R, Wechsler, 1981; Shinagawa et al., 1990), and the Wisconsin Card Sorting Test (WCST, Heaton, 1981; Kashima et al., 1987), was administered. Using these tests, we measured verbal memory, visual memory, general memory, attention/concentration, delayed recall (WMS-R), verbal intelligence quotient (IQ) and its six subtests, performance IQ and its five subtests, full-scale IQ (WAIS-R), and executive function (WCST). Outcome measures of the WCST comprised the number of categories achieved, total errors, and perseverative errors. Perseverative errors included two types of perseveration: inappropriate repetitions of a response that sticks to the previously achieved category (i.e., perseverative errors of Milner type; PEM) and repetitions of the immediately preceding incorrect response (i.e., perseverative errors of Nelson type; PEN). The WMS-R, WAIS-R and WCST were completed by 415 (92.0%), 379 (84.0%) and 408 (90.5%) of the total 451 participants, respectively.

### 2.4. Analysis

Information on the date of birth was obtained for all participants. Based on this information, two types of the four seasons were considered; one criterion (“Traditional criterion”) was the traditional Japanese definition of the four seasons (i.e., March, April and May into spring; June, July and August into summer; September, October and November into autumn; December, January and February into winter), and the other criterion (“Astronomical criterion”) was the definition of the four seasons taking account of the equinoxes (i.e., March 22–June 21 into spring; June 22–September 21 into summer; September 22–December 21 into autumn; December 22–March 21 into winter). We herein considered these two definitions of the four seasons because previous studies investigating the association between season of birth and schizophrenia/schizotypy have employed different definitions, such that some have used the Traditional criterion (e.g., Takei et al., 1995; Kunugi et al., 1997) while others the Astronomical criterion (e.g., Reid and Zborowski, 2006; Cohen and Najolia, 2011). In the present report, the Traditional criterion was used unless otherwise specified and the Astronomical criterion was used for confirmation purpose.

Averages are reported as means  $\pm$  Standard deviation (S.D.). Categorical variables were compared using the  $\chi^2$  test. The *t*-test or analysis of variance (ANOVA) was used to examine differences between groups. Pearson's *r* was used to examine correlations. Partial correlation analysis was used to examine correlations, controlling for potentially confounding variables. The analysis of covariance (ANCOVA) was performed to compare scores controlling for confounders as defined below. Statistical significance was set at two-tailed  $p < 0.05$ . Analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 18.0 (SPSS Japan, Tokyo).

### 3. Results

#### 3.1. Demographic characteristics and schizotypal personality

Of the 451 participants, 112 were male and 339 female. Mean age of the participants was  $45.2 \pm 15.2$  years. Mean years of education was  $14.9 \pm 2.6$ . Numbers of participants who were born in spring, summer, autumn and winter (based on the “Traditional criterion”) were 98, 113, 106 and 134, respectively. There were no significant differences in age [ $F(3,447) = 0.10, p = 0.96$ ] or sex [ $\chi^2(3) = 6.02, p = 0.11$ ] distribution depending on season of birth. Numbers of participants who were born in January, February, March, April, May, June, July, August, September, October, November and December were 42, 53, 41, 31, 26, 38, 32, 43, 32, 46, 28 and 39, respectively. There were no significant differences in age [ $F(11,439) = 1.52, p = 0.12$ ] or sex [ $\chi^2(11) = 12.5, p = 0.12$ ] distribution depending on month of birth. Mean scores of the cognitive–perceptual factor, interpersonal factor, disorganized factor, and the total SPQ score were  $4.0 \pm 4.2, 6.5 \pm 5.6, 3.4 \pm 3.2,$  and  $12.9 \pm 10.0,$  respectively. Males scored significantly higher than females in the interpersonal factor ( $t = 2.4, d.f. = 162, p = 0.016$ ), but they did not differ in the other two factors or the total SPQ score (all  $p > 0.3$ ). Age showed a significant negative correlation with the disorganized factor ( $r = -0.22, p < 0.001$ ) and total SPQ score ( $r = -0.12, p = 0.009$ ), while years of education did not show any significant correlations with the SPQ indices (all  $p > 0.3$ ). Therefore, we decided to control for age and sex in the ANCOVA model as these variables could potentially confound the association between season of birth and schizotypal traits.

#### 3.2. Correlations between schizotypal traits and temperament/character dimensions

Table 1 shows the partial correlations, controlling for age and sex, between the SPQ indices and seven dimensions of the TCI. The SPQ indices were positively correlated with harm avoidance and self-transcendence while they were negatively correlated with novelty seeking, reward dependence, self-directedness and cooperativeness.

#### 3.3. Association of season of birth with schizotypal trait, temperament/character, and cognitive function

Fig. 1 shows the relationship between birth season (based on the “Traditional criterion”) and the total SPQ score in the whole sample. Mean total SPQ scores of those born in spring, summer, autumn, and winter were  $12.6 \pm 9.3, 12.5 \pm 8.9, 11.0 \pm 9.7,$  and  $15.0 \pm 11.4,$  respectively. The ANCOVA, controlling for age and sex, revealed that the total SPQ score was significantly different between these four seasonal groups [ $F(3,445) = 3.6, p = 0.014$ ]; post-hoc analysis with Bonferroni correction revealed that the total SPQ score was significantly higher in those individuals born in winter than those born in autumn (estimated mean difference = 4.09, 95% confidence interval = 0.69 to 7.50,  $p = 0.009$ ). In addition, the total SPQ score was significantly higher in the winter-born individuals than in the remaining individuals ( $15.0 \pm 11.4$  vs.  $12.0 \pm 9.3$ ;  $t = 2.66, d.f. = 211,$

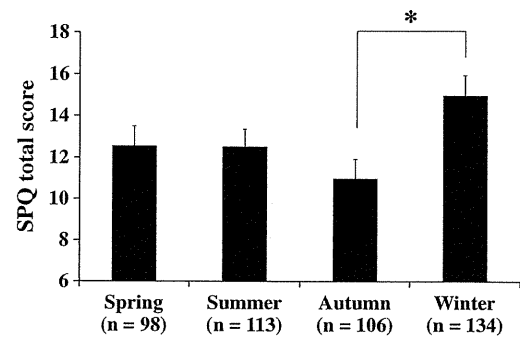


Fig. 1. Comparisons of the total SPQ score between individuals born in each of the four seasons (based on the Traditional criterion). \*  $p < 0.05$  (according to the ANCOVA with post-hoc analysis with Bonferroni correction).

$p = 0.008$ ). Taking into account that Lahti et al. (2009) found the significant association between winter/autumn birth and schizotypal traits only in women, the similar analyses, including the ANCOVA with age as a covariate and the  $t$ -test, were repeated separately for males and females. For males, the ANCOVA revealed that the main effect of season of birth was not significant [ $F(3,107) = 0.86, p = 0.46$ ]. The total SPQ score was not significantly different between winter-born men and the remaining men ( $15.1 \pm 11.4$  vs.  $13.1 \pm 10.7$ ;  $t = 0.85, d.f. = 110, p = 0.40$ ). For females, the ANCOVA revealed that the total SPQ score was significantly different between these four seasonal groups [ $F(3,334) = 3.9, p = 0.009$ ]; post-hoc analysis with Bonferroni correction revealed that the total SPQ score was significantly higher in those individuals born in winter than those born in autumn (estimated mean difference = 4.64, 95% confidence interval = 0.86 to 8.43,  $p = 0.007$ ). The total SPQ score was significantly higher in the winter-born women than in the remaining women ( $14.9 \pm 11.4$  vs.  $11.6 \pm 8.7$ ;  $t = 2.94, d.f. = 162.5, p = 0.009$ ).

When the Astronomical criterion was used, mean total SPQ scores of those born in spring, summer, autumn, and winter were  $12.3 \pm 8.3, 12.4 \pm 9.7, 11.6 \pm 9.0,$  and  $14.8 \pm 11.8,$  respectively. The similar ANCOVA again revealed the significant difference in the total SPQ score between these four seasonal groups [ $F(3,445) = 3.0, p = 0.029$ ]; post-hoc analysis with Bonferroni correction revealed that the total SPQ score was significantly higher in those individuals born in winter than those born in autumn (estimated mean difference = 3.53, 95% confidence interval = 0.15 to 6.91,  $p = 0.035$ ). The total SPQ score was significantly higher in the winter-born individuals than in the remaining individuals ( $14.8 \pm 11.8$  vs.  $12.1 \pm 9.0$ ;  $t = 2.65, d.f. = 206, p = 0.018$ ).

Supplementary Fig. 1 shows the relationship between birth month and the total SPQ score in the whole sample. This figure also presents the deviance of temperature of each month from the annual average temperature in Tokyo (calculated as “average temperature of individual month” – “annual average temperature”) averaged between 1970 and 2000 according to statistics reported by the Japan Meteorological Agency; thus, peaks and valleys of this line graph indicate severe and mild climates, respectively. In this figure we can

Table 1

Partial correlations between schizotypal personality and temperament/character dimensions, controlling for age and sex ( $n = 443$ ).

	Novelty seeking	Harm avoidance	Reward dependence	Persistence	Self-directedness	Cooperativeness	Self-transcendence
Cognitive–perceptual factor	–0.08	0.15**	–0.19***	0.11*	–0.38***	–0.19***	0.37***
Interpersonal factor	–0.24***	0.53***	–0.37***	–0.03	–0.58***	–0.37***	0.02
Disorganized factor	–0.03	0.28***	–0.24***	0.01	–0.47***	–0.24***	0.14**
Total SPQ score	–0.16**	0.40***	–0.31***	0.02	–0.56***	–0.30***	0.21***

Each figure represents partial correlation coefficient ( $r$ ) ( $d.f. = 439$ ).

- \*  $p < 0.05$  (2-tailed).
- \*\*  $p < 0.01$  (2-tailed).
- \*\*\*  $p < 0.001$  (2-tailed).



**Table 2**

Partial correlations of SPQ three factors and total score with neurocognitive test results, controlling for age and sex.

	Verbal memory <sup>a</sup>	Visual memory <sup>a</sup>	General memory <sup>a</sup>	Attention/concentration <sup>a</sup>	Delayed recall <sup>a</sup>	Information <sup>b</sup>	Digit span <sup>b</sup>	Vocabulary <sup>b</sup>	Arithmetic <sup>b</sup>	Comprehension <sup>b</sup>
Cognitive-perceptual factor	−0.05	−0.06	−0.03	−0.08	−0.03	−0.05	0.01	0.00	−0.02	−0.06
Interpersonal factor	−0.08	−0.02	−0.07	−0.02	−0.02	−0.05	−0.02	−0.04	−0.06	−0.14**
Disorganized factor	−0.05	−0.06	−0.06	−0.08	−0.04	−0.03	−0.06	−0.01	−0.08	−0.11*
Total SPQ score	−0.07	−0.06	−0.07	−0.06	−0.03	−0.06	−0.02	−0.02	−0.07	−0.13*

Each figure represents partial correlation coefficient (*r*).\**p*<0.05; \*\**p*<0.01 (2-tailed).<sup>a</sup> *n* = 415, d.f. = 411.<sup>b</sup> *n* = 379, d.f. = 375.<sup>c</sup> *n* = 408, d.f. = 404.

see the general tendency that the higher bars correspond to the peaks of the line graph, indicating that those born in more severe climates, i.e., January, August and December, demonstrated greater schizotypal traits. Indeed, correlation between the temperature deviance from the annual average and the SPQ total score was significant ( $r=0.10$ ,  $p=0.028$ ).

Supplementary Figs. 2–5 show the relationships of four birth seasons (based on the “Traditional criterion”) with seven dimensions of the TCI (Fig. S2), five memory indices as measured by the WMS-R (Fig. S3), three IQ indices as measured by the WAIS-R (Fig. S4), and four indices of executive function as measured by the WCST (Fig. S5). The ANCOVA controlling for age and sex showed that the four seasonal groups did not differ in any of the seven TCI dimensions (all  $p>0.1$ ) or in any of the neurocognitive test results (i.e., indices of the WMS-R, WAIS-R, and WCST) (all  $p>0.05$ ). These relationships remained non-significant when the same analyses were repeated using the “Astronomical criterion” of season.

#### 3.4. Relationships of schizotypal trait with cognitive function

Table 2 presents correlations between the SPQ indices and cognitive test results, controlling for age and sex. Comprehension and digit symbol subtests of the WAIS-R showed significant, albeit weak (correlation coefficients ranging from −0.11 to −0.14), negative correlations with the interpersonal and disorganized factors and the total SPQ score, while there were no significant correlations of memory indices of the WMS-R or executive function indices of the WCST with any indices of the SPQ.

#### 3.5. Relationships of temperament/character with cognitive function

Table 3 shows correlations between the seven TCI dimensions and cognitive test results, controlling for age and sex. Harm avoidance was significantly negatively, while self-directedness and cooperativeness were significantly positively, associated with several memory and IQ measures including verbal memory, general memory, and a number of

IQ subtests, especially those belonging to verbal IQ. Persistence was associated with better performance on the WCST.

## 4. Discussion

We can summarize the main findings as follows. A significant association of schizotypal traits with winter birth was found, while season of birth was not significantly associated with any of the TCI dimensions or neurocognitive test results. We also found significant but mild relationships between higher SPQ scores and lower performance in two subtests of IQ.

The majority of studies in schizophrenia, in particular those conducted in the Northern Hemisphere, have reported that there is a winter (or winter/early spring) birth excess (Torrey et al., 1997; Davies et al., 2003), and such birth seasonality has also been found in Japanese patients (Kunugi et al., 1997; Tatsumi et al., 2002). However, this season of birth effect has not been replicated in the Southern Hemisphere (reviewed in McGrath and Welham, 1999). Taking into account that the countries in the Southern Hemisphere where these studies have been conducted are closer to the equator than those in the Northern Hemisphere, one of the possible explanations for this discrepancy is considered to relate to the latitude, i.e., the higher the latitude, the greater the season of birth effect (McGrath and Welham, 1999; Davies et al., 2003). The observed association between winter birth and greater SPQ score in our non-clinical population is compatible with the evidence in schizophrenia obtained in the Northern Hemisphere, supporting the dimensionality between schizotypal personality and schizophrenia. The present result of the significant association in women also accords with a recent study in Finland showing that winter/autumn birth in women predicts augmented schizotypal traits in adulthood (Lahti et al., 2009). For men, however, the absence of a significant association between winter birth and SPQ score in the present study might be due to the type II error since the mean total SPQ score was higher in winter-born men than in the remaining men (i.e.,  $15.1 \pm 11.4$  vs.  $13.1 \pm 10.7$ ). On the other hand, as mentioned earlier, findings from the three other precedent studies that have investigated the season of birth effect on

**Table 3**

Partial correlations between TCI seven dimensions and neurocognitive test results, controlling for age and sex.

	Verbal memory <sup>a</sup>	Visual memory <sup>a</sup>	General memory <sup>a</sup>	Attention/concentration <sup>a</sup>	Delayed recall <sup>a</sup>	Information <sup>b</sup>	Digit span <sup>b</sup>	Vocabulary <sup>b</sup>	Arithmetic <sup>b</sup>	Comprehension <sup>b</sup>
Novelty seeking	0.06	0.00	0.07	−0.09	−0.01	0.05	−0.05	0.07	−0.01	0.14**
Harm avoidance	−0.15**	0.01	−0.14**	−0.01	−0.09	−0.04	−0.01	−0.05	−0.08	−0.14**
Reward dependence	0.03	0.05	0.03	−0.04	0.03	−0.10	0.04	−0.08	−0.05	−0.02
Persistence	−0.01	−0.04	0.02	0.00	0.00	−0.01	0.04	0.04	0.01	0.06
Self-directedness	0.13**	0.02	0.12*	0.06	0.12*	0.08	0.07	0.09	0.14**	0.20***
Cooperativeness	0.12*	0.03	0.10*	0.01	0.07	0.03	0.09	0.09	0.00	0.13*
Self-transcendence	−0.03	−0.07	−0.01	−0.01	−0.02	−0.06	0.04	0.03	−0.04	−0.04

Each figure represents partial correlation coefficient (*r*).\**p*<0.05; \*\**p*<0.01; \*\*\**p*<0.001 (2-tailed).<sup>a</sup> *n* = 409, d.f. = 405.<sup>b</sup> *n* = 376, d.f. = 372.<sup>c</sup> *n* = 402, d.f. = 398.

Similarities <sup>b</sup>	Picture completion <sup>b</sup>	Picture arrangement <sup>b</sup>	Block design <sup>b</sup>	Object assembly <sup>b</sup>	Digit symbol <sup>b</sup>	Verbal IQ <sup>b</sup>	Performance IQ <sup>b</sup>	Full-scale IQ <sup>b</sup>	WCST category <sup>c</sup>	WCST total errors <sup>c</sup>	WCST PEM <sup>c</sup>	WCST PEN <sup>c</sup>
−0.10	0.02	0.02	−0.04	−0.04	−0.08	−0.06	−0.03	−0.05	0.01	−0.03	0.02	−0.02
−0.09	−0.03	0.02	−0.06	0.02	−0.11*	−0.10	−0.03	−0.08	0.00	−0.02	0.02	−0.05
−0.07	−0.03	0.00	−0.01	0.01	−0.14**	−0.08	−0.04	−0.07	−0.01	−0.02	0.02	0.01
−0.10	−0.02	0.02	−0.04	0.00	−0.13**	−0.10	−0.04	−0.08	0.00	−0.03	0.02	−0.02

schizotypy are not in line with the present one; two studies (Reid and Zborowski, 2006; Kirkpatrick et al., 2008) reported different relationships between season of birth and schizotypy from the present one, and one study (Cohen and Najolia, 2011) did not find any such significant association although this study observed that no less than 60% of individuals within the schizotypy group reporting a diagnosis of schizophrenia or prior hospitalization had been born during winter months. Given that the four studies (Reid and Zborowski, 2006; Kirkpatrick et al., 2008; Lahti et al., 2009) including the present one that found any significant relationship between season of birth and schizotypy were conducted in higher latitude regions of 35° to 60° whereas the study by Cohen and Najolia (2011) was conducted in a subtropical region with relatively mild winters, this discrepancy may have stemmed, at least partly, from the differences in latitude, as in the aforementioned schizophrenia literature.

Possible mechanisms underlying the association between season of birth and schizophrenia have been speculated, and a variety of seasonal factors, such as ambient temperature, viral infections (e.g., influenza) and vitamins, have been implicated (reviewed in Tochigi et al., 2004). Among these, the ambient temperature might be a promising factor that explains the winter/early spring birth excess in schizophrenia patients (Tochigi et al., 2004). We found that January, August and December, when the ambient temperature is either extremely hot or cold, were the top three months in terms of the increased likelihood of giving birth to those with greater schizotypal traits. In keeping with this, a summer birth excess in patients with deficit schizophrenia has been reported (Kirkpatrick et al., 2002; Messias et al., 2004).

Concerning the association between season of birth and temperamental/character personality dimensions, previous studies have reported significant effects of season of birth on certain temperament and/or character dimensions. Chotai et al. (2001) found in a Swedish adult cohort that those individuals born during February to April were significantly more likely than those born from October to January to have high novelty seeking among women and to have high persistence among men. Chotai et al. (2009) obtained a similar finding in a Finnish adult sample that women born in summer had significantly higher novelty seeking than women born in winter. By

contrast, Chotai et al. (2002) observed in Swedish adolescents that novelty seeking was significantly higher for females born from October to January as compared to females born otherwise. Kamata et al. (2009) found in a Japanese adult sample that higher ambient temperature at birth month was related to higher scores of self-directedness and persistence in females. These previous findings, though somewhat variable, suggest that certain temperamental/character dimensions could be affected by season of birth. In the present study, however, we did not find any significant association between season of birth and temperament/character dimensions. These varied findings may be due to sample characteristics (e.g., age, ethnicity, and geographic area), and more studies are therefore required to clarify this association.

Several lines of evidence have suggested that season of birth is also associated with cognitive function, although the findings are again mixed. Some studies reported that winter/spring birth was associated with better scores on the Wechsler Intelligence performance and full-scale IQs at age 7 (McGrath et al., 2006) and with higher proportion of expert chess players (Gobet and Chassy, 2008), whereas others found superior intellectual functioning in individuals born in summer (Gotoda, 1995; Bibby et al., 1996). In contrast, we did not observe any significant associations between season of birth and cognitive functioning. It should be noted, however, that the previous studies and the present one employed quite different samples and cognitive measures to assess participants' cognitive abilities.

We examined the correlation between schizotypal personality and temperament/character, and found a number of significant correlations between the three factors pertaining to schizotypy and temperament/character dimensions (Table 1). The results are largely consistent with those from two previous studies (Daneluzzo et al., 2005; Bora and Veznedaroglu, 2007), both of which demonstrated that cognitive-perceptual and disorganized factors of the SPQ correlated negatively with self-directedness and positively with self-transcendence, and that interpersonal factor of the SPQ correlated positively with harm avoidance and negatively with self-directedness.

With respect to the association between personality and cognitive function, we found significant but weak negative correlations between SPQ scores and comprehension and digit symbol subtests

Similarities <sup>b</sup>	Picture completion <sup>b</sup>	Picture arrangement <sup>b</sup>	Block design <sup>b</sup>	Object assembly <sup>b</sup>	Digit symbol <sup>b</sup>	Verbal IQ <sup>b</sup>	Performance IQ <sup>b</sup>	Full-scale IQ <sup>b</sup>	WCST category <sup>c</sup>	WCST total errors <sup>c</sup>	WCST PEM <sup>c</sup>	WCST PEN <sup>c</sup>
0.00	0.07	0.11*	0.01	0.09	−0.03	0.04	0.07	0.06	0.01	0.01	0.04	0.06
−0.03	−0.07	0.04	−0.07	−0.03	−0.08	−0.09	−0.05	−0.09	−0.06	0.06	0.02	−0.02
0.02	0.01	0.09	0.01	−0.02	0.00	−0.04	0.02	−0.01	0.00	0.02	0.04	0.04
0.04	0.08	0.01	0.02	−0.10*	0.07	0.05	0.00	0.03	0.12*	−0.13**	−0.11*	−0.08
0.16**	0.01	−0.06	0.10	−0.02	0.18***	0.18***	0.06	0.15**	0.05	−0.04	−0.03	0.02
0.15**	0.11*	0.02	0.11*	0.08	0.05	0.12*	0.09	0.13*	0.00	0.00	0.04	0.04
−0.02	0.06	0.03	0.06	−0.02	−0.01	−0.01	0.00	0.01	0.03	−0.02	0.00	0.03



of the WAIS-R. As described earlier, previous studies have demonstrated that schizotypal traits, even at a non-clinical level, are associated with mild impairments in cognitive domains including sustained attention, spatial working memory, and executive functioning. What is more relevant to the present finding is that recent studies have reported the association between psychometrically defined schizotypy and mild impairments in some aspects of IQ (Matheson and Langdon, 2008; Noguchi et al., 2008). In addition, the present finding may correspond well to the evidence that processing speed as measured by the digit symbol coding task is the most severely impaired cognitive domain in schizophrenia (Dickinson et al., 2007). In the present study, temperament/character dimensions, in particular harm avoidance, self-directedness and cooperativeness, were associated with performances on several cognitive domains including memory and IQ. In line with the present finding, previous studies have reported significant associations between higher self-directedness and cooperativeness on the one hand and better cognitive performance on the other (Bergvall et al., 2003; Smith et al., 2008).

Findings reported here should be considered in the context of a number of limitations. First, the present finding on the association between season of birth and schizotypy obtained in Japan may not be easily extrapolated to another location, particularly to the southern hemisphere. Second, given the high number of the correlational analyses between personality measures and cognitive indices (Tables 2 and 3), some stringent measures may have been needed to correct for the multiple testing. Nevertheless, we would like to note that our significant findings on the associations between specific personality traits and mildly impaired cognitive functioning were generally in harmony with previous ones (Bergvall et al., 2003; Matheson and Langdon, 2008; Noguchi et al., 2008; Smith et al., 2008), as discussed above. Third, since women were overrepresented in our sample, it is possible that the present findings are applicable only to women. The fourth limitation could be the relatively low mean total SPQ score of 12.9 (S.D. = 10.0) of our sample, given that the mean total SPQ scores of non-clinical populations have been reported to be around 20 in the majority of prior studies, most of which were conducted in Western countries. This discrepancy is likely to have been derived from ethnic differences (Western vs. Japanese/Asian). Indeed, mean total SPQ scores in healthy Japanese populations have been consistently shown to be relatively low, ranging from 8.1 to 12.9 (Someya et al., 1994; Wang et al., 2004; Hori et al., 2008a; Noguchi et al., 2008; Takahashi et al., 2010). Another plausible explanation for the discrepancy in SPQ scores between these samples might be the difference in mean age of participants, i.e., college students in most of the prior studies vs. adults in the present study. In a study of Chen et al. (1997), for example, mean total SPQ scores of Taiwanese adolescents and adults were 20.6 and 12.9, respectively. Thus, the present sample could be deemed representative of non-clinical Asian adults. Finally, although we targeted the adult population, most of the previous studies investigating the correlates of non-clinical schizotypy have targeted students. From the standpoint of the risk of developing schizophrenia, students may be a better suited population; however, we believe that our dimensional approach has its own merits. To further explore the dimensional model and to identify the risk population for the development of psychosis, future studies that investigate the association between season of birth and schizotypal traits among clinical populations (e.g., SPD patients with and without family history of schizophrenia) as well as student populations are needed.

In summary, the present study found that schizotypal traits in a non-clinical population were associated with an excess of winter birth, whereas season of birth was not significantly associated with temperament/character personality dimensions or neurocognition. Schizotypal traits were also associated with mild impairments in some aspects of intellectual functioning. These results point to the etiological similarity between schizotypal personality and schizo-

phrenia-spectrum disorders, potentially supporting the notion that these conditions are on the same continuum. From the perspective of public health, such attempts to identify early signs that confer vulnerability to schizotypy as well as schizophrenia-spectrum disorders might provide an important clue to prevention of and early intervention for schizophrenia.

#### Acknowledgements

We would like to thank all volunteers who participated in the study. This study was supported by Health and Labor Sciences Research Grants (Comprehensive Research on Disability, Health, and Welfare), Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (JSPS), Intramural Research Grant for Neurological and Psychiatric Disorders of NCNP, CREST, JST (H.K.), and Grant-in-Aid for Young Scientists from the JSPS (H.H.).

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.psychres.2011.07.028.

#### References

- American Psychiatric Association, 1987. *Diagnostic and Statistical Manual of Mental Disorders*, revised 3rd ed. American Psychiatric Association, Washington, D. C.
- Bergvall, A.H., Nilsson, T., Hansen, S., 2003. Exploring the link between character, personality disorder, and neuropsychological function. *European Psychiatry* 18, 334–344.
- Bibby, P.A., Lamb, S.J., Leyden, G., Wood, D., 1996. Season of birth and gender effects in children attending moderate learning difficulty schools. *British Journal of Educational Psychology* 66, 159–168.
- Bora, E., Veznedaroglu, B., 2007. Temperament and character dimensions of the relatives of schizophrenia patients and controls: the relationship between schizotypal features and personality. *European Psychiatry* 22, 27–31.
- Chen, W.J., Hsiao, C.K., Lin, C.C., 1997. Schizotypy in community samples: the three-factor structure and correlation with sustained attention. *Journal of Abnormal Psychology* 106, 649–654.
- Chotai, J., Forsgren, T., Nilsson, L.G., Adolfsson, R., 2001. Season of birth variations in the temperament and character inventory of personality in a general population. *Neuropsychobiology* 44, 19–26.
- Chotai, J., Jonasson, M., Hägglöf, B., Adolfsson, R., 2002. The Temperament Scale of Novelty Seeking in adolescents shows an association with season of birth opposite to that in adults. *Psychiatry Research* 111, 45–54.
- Chotai, J., Joukamaa, M., Taanila, A., Lichtermann, D., Miettinen, J., 2009. Novelty seeking among adult women is lower for the winter borns compared to the summer borns: replication in a large Finnish birth cohort. *Comprehensive Psychiatry* 50, 562–566.
- Claridge, G.S., 1985. *Origins of Mental Illness*. Blackwell, Oxford.
- Cloninger, C.R., 1987. A systematic method for clinical description and classification of personality variants. A proposal. *Archives of General Psychiatry* 44, 573–588.
- Cloninger, C.R., Svrakic, D.M., Przybeck, T.R., 1993. A psychobiological model of temperament and character. *Archives of General Psychiatry* 50, 975–990.
- Cohen, A.S., Najolia, G.M., 2011. Birth characteristics and schizotypy: evidence of a potential “second hit”. *Journal of Psychiatric Research* 45, 955–961.
- Daneluzzo, E., Bustini, M., Stratta, P., Casaccia, M., Rossi, A., 1998. Schizotypal Personality Questionnaire and Wisconsin Card Sorting Test in a population of DSM-III-R schizophrenic patients and control subjects. *Comprehensive Psychiatry* 39, 143–148.
- Daneluzzo, E., Stratta, P., Rossi, A., 2005. The contribution of temperament and character to schizotypy multidimensionality. *Comprehensive Psychiatry* 46, 50–55.
- Davies, G., Welham, J., Chant, D., Torrey, E.F., McGrath, J., 2003. A systematic review and meta-analysis of Northern Hemisphere season of birth studies in schizophrenia. *Schizophrenia Bulletin* 29, 587–593.
- Dickinson, D., Ramsey, M.E., Gold, J.M., 2007. Overlooking the obvious: a meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. *Archives of General Psychiatry* 64, 532–542.
- Folley, B.S., Park, S., 2005. Verbal creativity and schizotypal personality in relation to prefrontal hemispheric laterality: a behavioral and near-infrared optical imaging study. *Schizophrenia Research* 80, 271–282.
- Fujiwara, T., 1993. The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. *Advances in Schizophrenia Research* 3, 21–25 (in Japanese).
- Gobet, F., Chassy, P., 2008. Season of birth and chess expertise. *Journal of Biosocial Science* 40, 313–316.
- Gooding, D.C., Matts, C.W., Rollmann, E.A., 2006. Sustained attention deficits in relation to psychometrically identified schizotypy: evaluating a potential endophenotypic marker. *Schizophrenia Research* 82, 27–37.
- Gotoda, T., 1995. Born in summer? *Nature* 377, 672.
- Guilleme, F., Bicu, M., Semkovska, M., Debruille, J.B., 2002. The dimensional symptom structure of schizophrenia and its association with temperament and character. *Schizophrenia Research* 56, 137–147.

- Heaton, R.K., 1981. The Wisconsin Card Sorting Test (Manual). Psychological Assessment Resources, Florida.
- Hori, H., Ozeki, Y., Terada, S., Kunugi, H., 2008a. Functional near-infrared spectroscopy reveals altered hemispheric laterality in relation to schizotypy during verbal fluency task. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 32, 1944–1951.
- Hori, H., Noguchi, H., Hashimoto, R., Nakabayashi, T., Saitoh, O., Murray, R.M., Okabe, S., Kunugi, H., 2008b. Personality in schizophrenia assessed with the Temperament and Character Inventory (TCI). *Psychiatry Research* 160, 175–183.
- Hori, H., Teraishi, T., Ozeki, Y., Hattori, K., Sasayama, D., Matsuo, J., Kawamoto, Y., Kinoshita, Y., Higuchi, T., Kunugi, H., 2011. Schizotypal personality in healthy adults is related to blunted cortisol responses to the combined dexamethasone/corticotropin-releasing hormone test. *Neuropsychobiology* 63, 232–241.
- Kamata, M., Suzuki, A., Matsumoto, Y., Togashi, H., Otani, K., 2009. Effect of month of birth on personality traits of healthy Japanese. *European Psychiatry* 24, 86–90.
- Kashima, H., Handa, T., Kato, M., Sakura, K., Yokoyama, N., Murakami, M., Shigemori, K., Muramatsu, T., Saito, H., Ooe, Y., Mimura, M., Asai, M., Hosaki, H., 1987. Neuropsychological investigation on chronic schizophrenia—aspects of its frontal functions. In: Takahashi, R., Flor-Henry, P., Gruzelier, J., Niwa, S. (Eds.), *Cerebral Dynamics, Laterality and Psychopathology*. Elsevier, Amsterdam, pp. 337–345.
- Kendler, K.S., Ochs, A.L., Gorman, A.M., Hewitt, J.K., Ross, D.E., Mirsky, A.F., 1991. The structure of schizotypy: a pilot multitrait twin study. *Psychiatry Research* 36, 19–36.
- Kiang, M., Kutas, M., 2005. Association of schizotypy with semantic processing differences: an event-related brain potential study. *Schizophrenia Research* 77, 329–342.
- Kijima, N., Saito, R., Takeuchi, M., Yoshino, A., Ono, Y., Kato, M., Kitamura, T., 1996. Cloninger's seven-factor model of temperament and character and Japanese version of Temperament and Character Inventory (TCI). *Archives of Psychiatric Diagnostic and Clinical Evaluations* 7, 379–399 (in Japanese).
- Kijima, N., Tanaka, E., Suzuki, N., Higuchi, H., Kitamura, T., 2000. Reliability and validity of the Japanese version of the Temperament and Character Inventory. *Psychological Reports* 86, 1050–1058.
- Kirkpatrick, B., Tek, C., Allardyce, J., Morrison, G., McCreadie, R.G., 2002. Summer birth and deficit schizophrenia in Dumfries and Galloway, southwestern Scotland. *American Journal of Psychiatry* 159, 1382–1387.
- Kirkpatrick, B., Messias, E., LaPorte, D., 2008. Schizoid-like features and season of birth in a nonpatient sample. *Schizophrenia Research* 103, 151–155.
- Kunugi, H., Nanko, S., Hayashi, N., Saito, K., Hirose, T., Kazamatsuri, H., 1997. Season of birth of schizophrenics in a recent Japanese sample. *Psychiatry and Clinical Neurosciences* 51, 213–216.
- Lahti, J., Raikkönen, K., Sovio, U., Miettinen, J., Hartikainen, A.L., Pouta, A., Taanila, A., Joukamaa, M., Järvelin, M.R., Veijola, J., 2009. Early-life origins of schizotypal traits in adulthood. *British Journal of Psychiatry* 195, 132–137.
- Lenzenweger, M.F., 2001. Reaction time slowing during high-load, sustained-attention task performance in relation to psychometrically identified schizotypy. *Journal of Abnormal Psychology* 110, 290–296.
- Lenzenweger, M.F., Korfine, L., 1994. Perceptual aberrations, schizotypy, and the Wisconsin Card Sorting Test. *Schizophrenia Bulletin* 20, 345–357.
- Martin, R.P., Foels, P., Clanton, G., Moon, K., 2004. Season of birth is related to child retention rates, achievement, and rate of diagnosis of specific LD. *Journal of Learning Disabilities* 37, 307–317.
- Matheson, S., Langdon, R., 2008. Schizotypal traits impact upon executive working memory and aspects of IQ. *Psychiatry Research* 159, 207–214.
- McGrath, J.J., Welham, J.L., 1999. Season of birth and schizophrenia: a systematic review and meta-analysis of data from the Southern Hemisphere. *Schizophrenia Research* 35, 237–242.
- McGrath, J.J., Saha, S., Lieberman, D.E., Buka, S., 2006. Season of birth is associated with anthropometric and neurocognitive outcomes during infancy and childhood in a general population birth cohort. *Schizophrenia Research* 81, 91–100.
- Messias, E., Kirkpatrick, B., Bromet, E., Ross, D., Buchanan, R.W., Carpenter Jr., W.T., Tek, C., Kendler, K.S., Walsh, D., Dollfus, S., 2004. Summer birth and deficit schizophrenia: a pooled analysis from 6 countries. *Archives of General Psychiatry* 61, 985–989.
- Mitropoulou, V., Goodman, M., Sevy, S., Elman, I., New, A.S., Iskander, E.G., Silverman, J.M., Breier, A., Siever, L.J., 2004. Effects of acute metabolic stress on the dopaminergic and pituitary–adrenal axis activity in patients with schizotypal personality disorder. *Schizophrenia Research* 70, 27–31.
- Noguchi, H., Hori, H., Kunugi, H., 2008. Schizotypal traits and cognitive function in healthy adults. *Psychiatry Research* 161, 162–169.
- O'Driscoll, G.A., Lenzenweger, M.F., Holzman, P.S., 1998. Antisaccades and smooth pursuit eye tracking and schizotypy. *Archives of General Psychiatry* 55, 837–843.
- Otsubo, T., Tanaka, K., Koda, R., Shinoda, J., Sano, N., Tanaka, S., Aoyama, H., Mimura, M., Kamijima, K., 2005. Reliability and validity of Japanese version of the Mini-International Neuropsychiatric Interview. *Psychiatry and Clinical Neurosciences* 59, 517–526.
- Park, S., McTigue, K., 1997. Working memory and the syndromes of schizotypal personality. *Schizophrenia Research* 26, 213–220.
- Raine, A., 1991. The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. *Schizophrenia Bulletin* 17, 555–564.
- Raine, A., Reynolds, C., Lencz, T., Scerbo, A., Tripthon, N., Kim, D., 1994. Cognitive-perceptual, interpersonal, and disorganized features of schizotypal personality. *Schizophrenia Bulletin* 20, 191–201.
- Raine, A., Lencz, T., Mednick, S.A., 1995. *Schizotypal Personality*. Cambridge University Press, Cambridge.
- Reid, H.M., Zborowski, M.J., 2006. Schizophrenia-proneness, season of birth and sleep: elevated schizotypy scores are associated with spring births and extremes of sleep. *Personality and Individual Differences* 41, 1185–1193.
- Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry* 59 (suppl. 20), 22–57.
- Shinagawa, F., Kobayashi, S., Fujita, K., Maekawa, H., 1990. Japanese Wechsler Adult Intelligence Scale-Revised. Nihonbunkakagakusha, Tokyo, in Japanese.
- Siever, L.J., Davis, K.L., 2004. The pathophysiology of schizophrenia disorders: perspectives from the spectrum. *American Journal of Psychiatry* 161, 398–413.
- Smith, M.J., Cloninger, C.R., Harms, M.P., Csernansky, J.G., 2008. Temperament and character as schizophrenia-related endophenotypes in non-psychotic siblings. *Schizophrenia Research* 104, 198–205.
- Someya, T., Sasaki, T., Hosoda, S., Takahashi, S., 1994. Reliability and validity of schizotypal personality questionnaire. *Archives of Psychiatric Diagnostic and Clinical Evaluations* 5, 98 (in Japanese).
- Sugishita, M., 2001. Japanese Wechsler Memory Scale-Revised. Nihonbunkakagakusha, Tokyo, in Japanese.
- Svrakic, D.M., Whitehead, C., Przybeck, T.R., Cloninger, C.R., 1993. Differential diagnosis of personality disorders by the seven-factor model of temperament and character. *Archives of General Psychiatry* 50, 991–999.
- Takahashi, H., Iwase, M., Canuet, L., Yasuda, Y., Ohi, K., Fukumoto, M., Iike, N., Nakahachi, T., Ikezawa, K., Azechi, M., Kurimoto, R., Ishii, R., Yoshida, T., Kazui, H., Hashimoto, R., Takeda, M., 2010. Relationship between prepulse inhibition of acoustic startle response and schizotypy in healthy Japanese subjects. *Psychophysiology* 47, 831–837.
- Takei, N., Sham, P., Callaghan, E., Glover, G., Murray, R., 1995. Early risk factors in schizophrenia: place and season of birth. *European Psychiatry* 10, 165–170.
- Tatsumi, M., Sasaki, T., Iwanami, A., Kosuga, A., Tanabe, Y., Kamijima, K., 2002. Season of birth in Japanese patients with schizophrenia. *Schizophrenia Research* 54, 213–218.
- Tochigi, M., Okazaki, Y., Kato, N., Sasaki, T., 2004. What causes seasonality of birth in schizophrenia? *Neuroscience Research* 48, 1–11.
- Torrey, E.F., Miller, J., Rawlings, R., Yolken, R.H., 1997. Seasonality of births in schizophrenia and bipolar disorder: a review of the literature. *Schizophrenia Research* 28, 1–38.
- Wang, J., Miyazato, H., Hokama, H., Hiramatsu, K., Kondo, T., 2004. Correlation between P50 suppression and psychometric schizotypy among non-clinical Japanese subjects. *International Journal of Psychophysiology* 52, 147–157.
- Wechsler, D., 1981. *Wechsler Adult Intelligence Scale, Revised*. Psychological Corporation, New York.
- Wechsler, D., 1987. *Wechsler Memory Scale Manual, Revised*. Psychological Corporation, San Antonio.

