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Original Paper

Neuropsychobiology

Neuropsychobiology 2009;59:234–238
DOI: 10.1159/000226612

Received: October 10, 2008
Accepted after revision: May 4, 2009
Published online: July 2, 2009

Orphan Nuclear Receptor Rev-erb Alpha Gene *(NR1D1)* and Fluvoxamine Response in Major Depressive Disorder in the Japanese Population

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Key Words
Major depressive disorder · Orphan nuclear receptor Rev-erbα gene, *NR1D1* · Fluvoxamine · Linkage disequilibrium · Tagging SNP · Clock genes · Circadian rhythm

Abstract
Background: Sleep-wake disturbance, frequently observed in major depressive disorder (MDD), negatively influences clinical status. Treatment with antidepressants also reportedly affects circadian rhythms. In a recent in vitro study, the nuclear receptor Rev-erbα was reported to be related to circadian rhythms, and was shown to be involved in the biological action of lithium therapy. Therefore, we examined the association between the orphan nuclear receptor Rev-erbα gene *(NR1D1)* and the efficacy of fluvoxamine treatment in 118 Japanese patients with major depressive disorder. ***Methods:*** The scores of the MDD patients in this study on the 17 items of the Structured Interview Guide for the Hamilton Rating Scale for Depression (SIGH-D) were 12 or higher. We defined a clinical response as a decrease of more than 50% in baseline SIGH-D within 8 weeks and clinical remission as a SIGH-D score of less than 7 at 8 weeks. We selected 3 'tagging SNPs' in *NR1D1* for the following association analysis. ***Results:*** We did not detect a significant association between *NR1D1* and the fluvoxamine therapeutic response in MDD in allele/genotype-wise analysis or haplotype-wise analysis. ***Conclusion:*** Our results suggest that *NR1D1* does not play a major role in the therapeutic response to fluvoxamine in Japanese MDD patients. However, because our sample was small, a replication study using another population and a larger sample will be required for conclusive results.

Introduction

Sleep-wake disturbance, frequently observed in major depressive disorder (MDD), negatively affects the clinical status of patients. It has been suggested that abnormalities in circadian rhythms are related to the pathophysiology of MDD [1, 2]. The evidence for this relation has been discussed in more detail in our previous paper [3] and a review by Barnard and Nolan [4].

Selective serotonin reuptake inhibitors (SSRIs), which are major therapeutic agents for MDD, act on the presynaptic neurons to increase the extracellular serotonin level, and this mechanism is believed to relieve depressive

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symptoms. However, serotonin affects circadian rhythms [5], and SSRIs have also been reported to have circadian properties: SSRIs have a phase-shifting effect in rat suprachiasmatic nucleus neural firing [6] and change the expression of clock genes in the striatum and hippocampus of mice [7], suggesting that the SSRIs' antidepressive action also may be attributable to circadian mechanisms. In addition, the clock gene was reported to be associated with greater severity of insomnia during antidepressant treatment, a higher recurrence rate and reduced need for sleep in bipolar disorder patients [8–10]. Therefore, we considered that clock genes might be therapeutic targets of SSRIs.

In the mammalian circadian feedback loop, it is known that the CLOCK/Bmal1 heterodimer drives the transcription of multiple clock genes including *Cry*, *Per* and Rev-erbα gene *(NR1D1)* through E-box elements (detailed evidence for the molecular clock mechanism in mammals has been discussed in several reviews [4, 11–13]). Recently, orphan nuclear receptor Rev-erbα and glycogen synthase kinase-3β (GSK-3β) were shown to be important circadian components [14]. Orphan nuclear receptor Rev-erbα, which belongs to the rev-erb family of transcription factors called 'orphan nuclear receptors', is a key negative-feedback regulator of the circadian clock, and is itself expressed in a circadian manner that is finely controlled both transcriptionally and post-transcriptionally [14, 15]. For example, orphan nuclear receptor Rev-erbα represses Bmal1 gene transcription [15]. Yin et al. [14] showed that orphan nuclear receptor Rev-erbα is a target of GSK-3β kinase activity, which is needed to mediate the regulation of circadian rhythms. These authors also found that in cultured mammalian cells, lithium treatment leads to rapid proteasomal degradation of Rev-erbα and subsequent activation of the Bmal1 gene, a clock gene [14]. Therefore, we thought that *NR1D1* was a good candidate gene for the pathophysiology of mood disorders, and performed an association analysis of *NR1D1* and mood disorders in the Japanese population [3]. No association was found [3], suggesting the possibility that MDD and the antidepressant treatment response in MDD do not have common susceptibility genes. Evidence in support of this hypothesis has been reported (e.g. *DTNBP1* and *NGFR*) [16, 17]. Therefore, although *NR1D1* was not found to play a major key role in the pathophysiology of mood disorders [3], we considered that *NR1D1* might be a susceptibility gene for SSRI treatment response.

In the present study, we examined the association between *NR1D1* and the efficacy of fluvoxamine treatment in Japanese MDD patients.

Materials and Methods

Subjects

The subjects were 118 MDD patients (59 males and 59 females: mean age ± SD 44.5 ± 16.5 years). All subjects were unrelated to each other, ethnically Japanese and lived in the central area of Japan. The patients were diagnosed according to DSM-IV criteria with consensus of at least 2 experienced psychiatrists on the basis of a review of medical records. Although these subjects were part of the MDD subject group in our previous study [3], all MDD patients in this study have specific characteristics: being treated with fluvoxamine and undergone a semi-structured interview for assessment of treatment response. Detailed information can be seen in 'Data collection'.

Fluvoxamine was taken 2 or 3 times a day for 8 weeks. The initial total dose in 1 day was 50–100 mg. Fluvoxamine was increased gradually to a maximum of 150 mg, depending on the patient's condition. Patients with insomnia and severe anxiety were prescribed benzodiazepine drugs, but no other psychotropic drugs were permitted during the study. The study was described to subjects and written informed consent was obtained from each participant. This study was approved by the Ethics Committee at Fujita Health University.

Data Collection

The scores of the MDD patients in this study on the 17 items of the Structured Interview Guide for the Hamilton Rating Scale for Depression (SIGH-D) were 12 or higher [18]. We defined a clinical response as a decrease of more than 50% in baseline SIGH-D within 8 weeks and clinical remission as a SIGH-D score of less than 7 at 8 weeks. Detailed information on data collection was described in a previous paper [19]. The clinical characteristics of patients in this study, classified according to these definitions, can be seen in table 1.

SNP Selection and Linkage Disequilibrium Evaluation

We first consulted the HapMap database (release 20/phase II, Jan 2006, www.hapmap.org; population: Japan Tokyo, minor allele frequencies of >0.05) and included 5 SNPs covering *NR1D1* [5′-flanking regions including about 750 bp from the initial exon and about 1 kb downstream (3′) from the last exon: HapMap database contig number chr17: 35501880–35510616]. Then 3 tagging SNPs were selected with the criteria of r^2 threshold greater than 0.8 in 'pair-wise tagging only' mode using the Tagger program (Paul de Bakker, www.broad.mit.edu/mpg/tagger) in Haploview [20]. These 3 tagging SNPs (rs939347, rs2071427 and rs3744805) were used for the following association analysis. Detailed information can be seen in our previous paper [3].

SNP Genotyping

We used TaqMan assays (Applied Biosystems, Foster City, Calif., USA) for all SNPs. Detailed information can be seen in our previous paper [3].

Statistical Analysis

Genotype deviation from the Hardy-Weinberg equilibrium was evaluated by the χ^2 test (SAS/Genetics, version 8.2, SAS Japan, Tokyo, Japan).

Marker-trait association analysis was used to evaluate allele- and genotype-wise association with the χ^2 test or Fisher's exact

Table 1. Clinical characteristics of the patients in both groups

	Total	Males	Females	Age years	Baseline SIGH-D	Fluvoxamine dose at 8 weeks mg/day	Number of previous episodes
Overall	118	59	59	44.5 ± 16.5	20.2 ± 5.88	122 ± 40.9	1.39 ± 0.658
Clinical response group[1]							
Responders	59	31	28	44.4 ± 16.3	21.5 ± 6.19	118 ± 41.1	1.36 ± 0.574
Nonresponders	59	28	31	44.3 ± 17.3	18.8 ± 5.28	125 ± 40.7	1.43 ± 0.774
p value		0.644		0.801	0.0145	0.391	0.480
Clinical remission group[2]							
Remitters	45	22	23	43.7 ± 15.9	19.6 ± 5.06	113 ± 43.9	1.37 ± 0.598
Nonremitters	73	37	36	45.1 ± 17.1	20.5 ± 6.34	127 ± 38.2	1.41 ± 0.715
p value		0.757		0.750	0.750	0.101	0.856

Average values presented with SD. [1] A decrease of ≥50% in baseline SIGH-D score. [2] Final SIGH-D score <7.

test (SAS/Genetics), and haplotype-wise association analysis was conducted with a likelihood ratio test using the Cocaphase 2.403 program [21]. The power calculation was performed using the Genetic Power Calculator [22]. In addition, we included another test for the association between percentage decrease from baseline to the end of the period of observation at the SIGH-D score and each tagging SNP genotype data, with analysis of covariance (ANCOVA) using the least-squares method. Gender, age at the time of recruitment, fluvoxamine dose at 8 weeks and SIGH-D total score at the baseline were covariates used in the analysis to better model the effect of genotype on percentage decrease from baseline to the end of the period of observation at the SIGH-D score. The statistical package JMP for Windows was used for ANCOVA (JMP 5.0. 1J, SAS). Bonferroni's correction was used to control inflation of the type I error rate. The significance level for all statistical tests was 0.05.

Results

Among the clinical characteristics of patients in this study, only 1 difference with total SIGH-D score at the baseline was detected ($p = 0.0145$; table 1). Genotype frequencies of all SNPs were in Hardy-Weinberg equilibrium. We did not detect an association between *NR1D1* and the fluvoxamine therapeutic response in MDD in the allele/genotype-wise analysis (table 2) or the haplotype analysis (response: $p = 0.695$, and remission: $p = 0.384$). Also, ANCOVA was performed to test the effect of the tagging SNP genotype at percentage decrease from baseline to the end of the period of observation with the SIGH-D score when MDD patients were treated with fluvoxamine. There were no statistically significant differences in the change in percentage decrease from baseline to the end of the period of observation with the SIGH-D score in which there was a fluvoxamine response to *NR1D1* genotype (rs939347: $p = 0.434$, rs2071427: $p = 0.891$, and rs3744805: $p = 0.450$).

Discussion

We first performed an association analysis of clock genes with fluvoxamine response in MDD patients. However, we did not detect a significant association between *NR1D1* and the fluvoxamine therapeutic response in MDD in allele/genotype-wise analysis or haplotype-wise analysis. In addition, we performed another test for the differences in percentage decrease from baseline to the end of the period of observation. In this test, we used the SIGH-D score among the data for each tagging SNP genotype that was evaluated by ANCOVA after adjustment for sex, age at the time of recruitment, fluvoxamine dose at 8 weeks and SIGH-D total score at the baseline. No association was found. Therefore, our results suggest that *NR1D1* does not play a major role in the therapeutic response to fluvoxamine in Japanese MDD patients.

We recently reported that *NR1D1* does not play a major role in the pathophysiology of Japanese MDD patients [3]. We consider that the present study strongly supports our previous study. However, because 1 of the biological actions of lithium treatment has been reported to affect the expression of clock genes mediated by Rev-erbα in vitro [14], the pharmacogenomics of bipolar disorder (lithium response) and gene-gene interactions among clock genes will also need to be investigated in the future.

Table 2. Genotype and allele distributions of *NR1D1* in both groups

	Clinical groups	Minor allele frequency	n	Genotype distribution			HWE	p value (HWE)	
				M/M	M/m	m/m		genotype	allele
SNP ID (major allele→minor allele)									
rs939347	responders	0.551	59	14	25	20	0.270		
G→A	nonresponders	0.475	59	16	30	13	0.880	0.355	0.241
	remission	0.522	45	12	19	14	0.302		
	nonremission	0.507	73	18	36	19	0.908	0.740	0.818
rs2071427	responders	0.542	59	11	32	16	0.477		
A→G	nonresponders	0.483	59	15	31	13	0.689	0.625	0.362
	remission	0.500	45	12	21	12	0.655		
	nonremission	0.521	73	14	42	17	0.192	0.483	0.759
rs3744805	responders	0.424	59	20	28	11	0.828		
A→G	nonresponders	0.483	59	15	31	13	0.689	0.596	0.360
	remission	0.478	45	14	19	12	0.302		
	nonresponders	0.438	73	21	40	12	0.335	0.307	0.555

M = Major allele; m = minor allele; HWE = Hardy-Weinberg equilibrium.

It will also be important to investigate the association between other clock genes and SSRIs response in MDD using larger samples.

A few points of caution should be noted in interpreting our results. Firstly, our sample sizes were small. We obtained power of more than 80% for the detection of association when we set the genotype relative risk at 1.55–1.85 in all 118 samples, under a multiplicative model of inheritance [22]. Therefore, a replication study using a larger sample may be required for conclusive results. Secondly, we did not include a mutation scan to detect rare variants with functional effects. However, it is difficult to evaluate the association of such extremely rare variants (e.g. minor allele frequencies of less than 0.01) from the viewpoint of power. Furthermore, the analysis of copy number variation, acetylation and methylation rates in *NR1D1* were not analyzed in our study.

In conclusion, our results suggest that *NR1D1* does not play a major role in the therapeutic response to fluvoxamine in Japanese MDD patients. However, because our sample was small, a replication study using another population and larger sample will be required for conclusive results.

Acknowledgments

We thank Ms. M. Miyata and Ms. S. Ishihara for their technical support. This work was supported in part by research grants from the Ministry of Education, Culture, Sports, Science and Technology, the Ministry of Health, Labor and Welfare, and the Japan Health Sciences Foundation (Research on Health Sciences focusing on Drug Innovation).

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Neuromol Med (2009) 11:53–57
DOI 10.1007/s12017-009-8060-7

ORIGINAL PAPER

CLOCK may Predict the Response to Fluvoxamine Treatment in Japanese Major Depressive Disorder Patients

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Received: 17 February 2009 / Accepted: 17 March 2009 / Published online: 4 April 2009

Abstract Recent studies have shown that selective serotonin reuptake inhibitors (SSRIs) have circadian properties, suggesting that the antidepressive action of SSRIs may also be attributable to circadian mechanisms. Another study reported an association between clock gene (*CLOCK*) and improvements in insomnia symptoms from SSRIs treatment. Therefore, we examined the association between *CLOCK* and the efficacy of fluvoxamine treatment in 121 patients with Japanese major depressive disorder (MDD). The MDD patients in this study had scores of 12 or higher on the 17 items of the Structured Interview Guide for Hamilton Rating Scale for Depression (SIGH-D). We defined a therapeutic response as a decrease of more than a 50% in baseline SIGH-D within 8 weeks, and clinical remission as a SIGH-D score of less than seven at 8 weeks. We selected three tagging SNPs in *CLOCK* for the subsequent statistical association analysis. We detected a significant association between rs3736544, a synonymous polymorphism in exon 20, and the fluvoxamine therapeutic response in MDD in the allele/genotype-wise analyses. In addition, remission with fluvoxamine was also significantly associated with rs3736544. These associations remained significant after Bonferroni correction. Moreover, haplotype analysis findings supported these significant associations, which appeared to be due mainly to rs3736544, in the fluvoxamine therapeutic remission. Our results indicate that *CLOCK* genotype may be a predictor of fluvoxamine treatment response in Japanese MDD. However, our sample size was small, and a replication study using larger samples may be required for conclusive results.

Keywords Major depressive disorder · *CLOCK* · Tagging SNPs · Fluvoxamine · SSRIs

Introduction

Major depressive disorder (MDD) patients commonly present not only abnormalities in sleep–wake rhythms but also disruptions in biological circadian rhythms. Therefore, disruptions in circadian rhythms have been suggested to be involved in the pathogenesis of MDD (Barnard and Nolan 2008; Kishi et al. 2008a, 2008b). All psychotropic drugs act on the systems of neurotransmitters such as dopamine and serotonin in the brain (Barnard and Nolan 2008), and recently these neurotransmitter systems have been reported to have reciprocal interactions with circadian rhythms (Monteleone and Maj 2008).

Selective serotonin reuptake inhibitors (SSRIs) such as fluvoxamine, which are major therapeutic agents for MDD, inhibit serotonin transport in the presynaptic neuron, and increase the extracellular serotonin level. This mechanism is believed to relieve depressive symptoms (Peveler and

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Kendrick 2005). On the other hand, many animal and in vitro studies have shown that serotonin directly affects circadian rhythms (Monteleone and Maj 2008), and SSRIs have also been reported to have circadian properties. SSRIs have a phase shifting effect in neural firing in the rat suprachiasmatic nucleus (Sprouse et al. 2006), and change the expression of clock genes in the striatum and hippocampus of mice (Uz et al. 2005), suggesting that the antidepressive action of SSRIs may also be attributable to circadian mechanisms. Therefore, we considered that clock genes might be therapeutic targets for SSRIs.

The clock gene (*CLOCK*, OMIM *601851, 25 exons in this genomic region spanning 115.138 kb), located on 4q12, is one of the major components of the cellular clock gene mechanism. It is known to be associated with human circadian preference (morningness/eveningness) (Katzenberg et al. 1998; Mishima et al. 2005). Several clinical subgroup analyses have shown a significant association between an SNP (rs1801260: T3111C) in *CLOCK* and sleep disregulation in mood disorders including MDD and bipolar disorder (BP) (Serretti et al. 2003) and a higher recurrence rate in BP (Benedetti et al. 2003). In addition, Serretti and colleagues reported an association between T3111C and improved insomnia from fluvoxamine or paroxetine treatment (Serretti et al. 2005). However, three genetic studies, including our previous study, reported no association between *CLOCK* and MDD (Bailer et al. 2005; Desan et al. 2000; Kishi et al. 2008a). Thus, there is disagreement in the results of these studies as to treatment response and the pathophysiology of MDD (Gratacos et al. 2008).

In this study, we examined the association between *CLOCK* and the efficacy of fluvoxamine treatment in Japanese MDD patients. To do this, we applied the recently recommended strategy of "gene-based" association analysis (Neale and Sham 2004).

Materials and Methods

Subjects

The subjects were 121 MDD patients (60 males and 61 females: mean age ± standard deviation (SD) 44.5 ± 16.5 years). All subjects were unrelated to each other, ethnically Japanese, and lived in the central area of Japan. The patients were diagnosed according to DSM-IV criteria with consensus of at least two experienced psychiatrists on the basis of a review of medical records. Fluvoxamine was taken two or three times a day for 8 weeks. The initial total dose was 50–100 mg per day, and the dosage was then increased gradually to a maximum of 150 mg, depending on the patients' condition. Patients with insomnia and severe anxiety were prescribed benzodiazepine drugs, but no other psychotropic drugs were permitted during the study. The study was described to subjects and written informed consent was obtained from each. This study was approved by the Ethics Committee at Fujita Health University.

Data Collection

The MDD patients in this study had scores of 12 or higher on the 17 items of the Structured Interview Guide for Hamilton Rating Scale for Depression (SIGH-D). Patients with this moderate range of severity tend to respond to antidepressants (Saito et al. 2006). We defined a therapeutic response as a decrease of more than 50% in baseline SIGH-D within 8 weeks, and a clinical remission as a SIGH-D score of less than 7 at 8 weeks. Detailed information on data collection was described in a previous paper (Saito et al. 2006). The clinical characteristics of the patients in this study, classified according to these definitions, can be seen in Table 1.

SNPs Selection and Linkage Disequilibrium (LD) Evaluation

We selected three "tagging SNPs" (rs3736544: synonymous polymorphism in exon 20, rs1801260: 3′ untranslated region (UTR) in exon 23, rs3749474: 3′ UTR in exon 23) in *CLOCK*. Detailed information can be seen in our previous paper (Kishi et al. 2008a).

SNPs Genotyping

We used TaqMan assays (Applied Biosystems, Inc., Foster City, CA,) for all SNPs. Detailed information can be seen in our previous paper (Kishi et al. 2008a).

Statistical Analysis

Genotype deviation from the Hardy–Weinberg equilibrium (HWE) was evaluated by chi-square test (SAS/Genetics, release 8.2, SAS Japan Inc, Tokyo, Japan).

Marker-trait association analysis was used to evaluate allele- and genotype-wise associations with the chi-square test (SAS/Genetics, release 8.2, SAS Japan Inc, Tokyo, Japan), and haplotype-wise association analysis was done with a likelihood ratio test using the COCAPHASE 2.403 program (Dudbridge 2003). Bonferroni's correction was used to control inflation of the type I error rate. Power calculation was performed using the Genetic Power Calculator (Purcell et al. 2003).

The significance level for all statistical tests was 0.05.

Table 1 Clinical characteristics of the patients in both definition groups

	N			Age (mean ± SD)	Baseline SIGH-D (avg ± SD)	Fluvoxamine dose at 8 weeks (mg/day) (avg ± SD)	Number of previous episode (avg ± SD)
	Total	Male	Female				
Overall	121	60	61	44.5 ± 16.5	20.2 ± 5.88	122 ± 40.9	1.39 ± 0.658
Clinical response group[a]							
Responders	60	31	29	44.4 ± 16.3	21.5 ± 6.19	118 ± 41.1	1.36 ± 0.574
Nonresponders	61	29	32	44.3 ± 17.3	18.8 ± 5.28	125 ± 40.7	1.43 ± 0.774
P-value	0.645			0.819	0.0145	0.391	0.480
Clinical remission group[b]							
Remitters	45	22	23	43.7 ± 15.9	19.6 ± 5.06	113 ± 43.9	1.37 ± 0.598
Nonremitters	76	38	38	45.1 ± 17.1	20.5 ± 6.34	127 ± 38.2	1.41 ± 0.715
P-value	0.722			0.750	0.750	0.101	0.856

[a] Clinical response was defined as a 50% or greater decrease in the baseline SIGH-D score

[b] Clinical remission was defined as a final SIGH-D score of less than seven

Results

The LD structures of *CLOCK* from the HapMap database were described in our previous paper (Kishi et al. 2008a). Among the clinical characteristics of the patients in this study, only one significant difference with total SIGH-D score was detected at the baseline in relation to fluvoxamine therapeutic response (*P*-value = 0.0145) (Table 1). Genotype frequencies of all SNPs were in HWE. We detected a significant association between rs3736544 and the fluvoxamine therapeutic response in MDD in the allele/genotype-wise analysis (Table 2). In addition, remission with fluvoxamine was significantly associated with rs3736544 (Table 2). Moreover, the significance of these associations remained after Bonferroni correction (Table 2). We also found an association between rs3749474 and the fluvoxamine therapeutic response in MDD in the genotype-wise analysis (*P*-value: 0.0251) (Table 2). However, this might have resulted from type I error due to multiple testing (*P*-value: 0.0752 after Bonferroni's correction) (Table 2). The haplotype-wise analysis provided evidence for a significant association that appears to be due mainly to rs3736544 in fluvoxamine therapeutic remission (Table 3).

Table 2 Association analysis of tagging SNPs in *CLOCK*

SNP[a]	Phenotype	MAF	*N*	Genotype distribution[b]			*P*-value[d]			Corrected *P*-value[d,e]	
				M/M	M/m	m/m	HWE[c]	Genotype	Allele	Genotype	Allele
rs3736544	Responders	0.267	60	30	28	2	0.135				
G > T	Nonresponders	0.115	61	48	12	1	0.804	**0.00434**	**0.00261**	**0.00130**	**0.00738**
	Remission	0.289	45	21	22	2	0.203				
	Nonremission	0.132	76	57	18	1	0.751	**0.00651**	**0.00257**	**0.0195**	**0.00771**
rs1801260	Responders	0.133	60	46	12	2	0.297				
T > C	Nonresponders	0.189	61	39	21	1	0.328	0.187	0.243		
	Remission	0.156	45	33	10	2	0.301				
	Nonremission	0.164	76	52	23	1	0.378	0.390	0.855		
rs3749474	Responders	0.417	60	19	32	9	0.452				
T > C	Nonresponders	0.336	61	27	27	7	0.949	0.358	0.196		
	Remission	0.467	45	12	24	9	0.632				
	Nonremission	0.322	76	34	35	7	0.637	0.0734	**0.0251**		0.0752

[a] major allele > minor allele

[b] M: major allele, m: minor allele

[c] HWE: Hardy–Weinberg equilibrium

[d] Bold numbers represent significant *P*-value

[e] Caluculated by Bonferroni's correction

Table 3 Haplotype-wise analysis of tagging SNPs in *CLOCK*

Common haplotypes rs3736544-rs1801260-rs3749474	Phenotype	Individual haplotype frequency	Individual *P*-value[a]	Phenotype	Global *P*-value[a]
GTT	Responders	0.600	0.173		
	Nonresponders	0.686		Responders	0.436
	Remission	0.548	**0.0191**	Nonresponders	
	Nonremission	0.703		Remission	**0.015**
GCC	Responders	0.146	0.401	Nonremission	
	Nonresponders	0.188			
	Remission	0.167	1.00		
	Nonremission	0.167			
TTC	Responders	0.255	**0.0137**		
	Nonresponders	0.125			
	Remission	0.286	**0.00417**		
	Nonremission	0.130			

[a] Bold numbers represent significant *P*-value

Discussion

In this study, we detected a significant association between rs3736544 in *CLOCK*, which is a synonymous polymorphism in exon 20, and the fluvoxamine therapeutic response and remission in the allele/genotype-wise analysis. This significance remained after Bonferroni correction. Haplotype analysis indicated three common haplotypes (rs3736544-rs1801260-rs3749474: GTT, GCC and TTC). Among them, the TTC haplotype was less prevalent in subjects with a fluvoxamine therapeutic response ($P = 0.0137$) and was associated with remission on fluvoxamine ($P = 0.00417$). The GTT haplotype was also significantly associated with remission on fluvoxamine ($P = 0.0191$). In a recent study, we selected six tagging SNPs among 106 SNPs covering all of *CLOCK*, including 5′-flanking regions about 2 kb upstream (5′) from the initial exon and about 5 kb downstream (3′) from the last exon (HapMap database contig number chr4: 55990340.. 56108588), with the criteria of an r^2 threshold greater than 0.8 in "pair-wise tagging only" mode using the Tagger program. LD structures of *CLOCK* from the HapMap database were described in our previous paper (Kishi et al. 2008a). However, the LD structure of *CLOCK* in our sample was very tight except for rs1801260 and rs3749474 (Kishi et al. 2008a). Also, the LD structures of MDD samples treated with fluvoxamine and control samples were almost the same (Kishi et al. 2008a). As these results show, rs3736544 covers a wide and important region including the exons and the promoter region in *CLOCK*. Therefore, it is possible that rs3736544 influences biological function in the brain. In previous genetic analyses of *CLOCK*, only T3111C (rs1801260) was selected. T3111C (rs1801260) has been detected at position 3111 in the *CLOCK* mRNA 3′ untranslated region, and was reported to be associated with a substantial delay in preferred timing for activity and sleep in a human study (Katzenberg et al. 1998). As for function, T3111C (rs1801260) has been speculated to affect mRNA (Katzenberg et al. 1998); however, one study with luciferase reported no significant effect on mRNA translatability from T3111C (Robilliard et al. 2002). We found an association of rs3736544 but not T3111C (rs1801260) with treatment outcome in this study. These findings suggest that functional analyses for other regions of the *CLOCK* should be performed in future studies.

A subgroup analysis has shown a significant association between an SNP (rs1801260: T3111C) in *CLOCK* and sleep disregulation in mood disorders (Serretti et al. 2003). Because benzodiazepine drugs are surely effective for insomnia and severe anxiety in MDD patients, which might mask the sleep disruption in MDD due to circadian abnormality, the analysis which takes the usage of benzodiazepines into account may also need to be carried out in the future. Because we had only a few MDD fluvoxamine treatment samples without benzodiazepine drugs, and we wanted to avoid statistical error, we did not perform such an analysis among these samples. Another subgroup analysis has shown a higher recurrence rate in BP in relation to T3111C (Benedetti et al. 2003), but we lacked data on recurrence in our sample, so we could not perform such analysis.

Our recent study found no association between *CLOCK* and MDD in the Japanese population (Kishi et al. 2008a). Thus, there is disagreement in the results among studies as to the treatment response and the pathophysiology of MDD (Gratacos et al. 2008).

A few points of caution should be noted in interpreting our results. First, it will be necessary to investigate the possibility that rs3736544 reflects biological function,

which we did not do in the present study. Second, we did not include a mutation scan to detect rare variants with functional effects. However, it is difficult to evaluate the association of such extremely rare variants (e.g., minor allele frequencies less than 0.01) from the viewpoint of power. Third, our sample sizes were small. A replication study using larger samples may be required for conclusive results.

In conclusion, our results indicate that *CLOCK* may be associated with fluvoxamine treatment outcome in Japanese MDD.

Acknowledgments We thank Ms. M. Miyata and Ms. S. Ishihara for their technical support. This work was supported in part by research grants from the Japan Ministry of Education, Culture, Sports, Science and Technology, the Ministry of Health, Labor and Welfare, and the Health Sciences Foundation (Research on Health Sciences focusing on Drug Innovation).

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Psychiatry Research: Neuroimaging 173 (2009) 206–211

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Gender difference in relationship between anxiety-related personality traits and cerebral brain glucose metabolism

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ARTICLE INFO

Article history:
Received 8 October 2007
Received in revised form 23 July 2008
Accepted 2 October 2008

Keywords:
TCI
Temperament
Anxiety
FDG-PET
Healthy subjects
Sex specificity

ABSTRACT

Recent functional neuroimaging studies have suggested that specific brain regions might be associated with the formation of anxiety-related personality traits, which are well known to be influenced by gender. Such anxiety-related personality traits are one of the representative predisposing factors for mood and anxiety disorders, whose incidence is also known to be much influenced by gender. However, little is known about the gender differences in brain function related to anxiety-related personality traits. The aim of the present study was to examine gender-related differences in the pattern of the relationships between an anxiety-related personality trait and cerebral brain glucose metabolism. Regional brain glucose metabolism was measured using [^{18}F]fluorodeoxyglucose positron emission tomography in 102 healthy subjects (65 males and 37 females). An anxiety-related trait was assessed using the Temperament and Character Inventory dimension Harm Avoidance (HA). HA was negatively correlated with glucose metabolism in the anterior portion of the ventromedial prefrontal cortex (vmPFC) in females but not in males. The anterior vmPFC may be a possible neural target for the prevention or therapy of emotional disorders, especially in females.

1. Introduction

It is well known that, in addition to individual differences, there is also a gender-related difference in the formation of personality. Previous studies of gender-related differences in personality have focused especially on anxiety-related personality traits such as Neuroticism in the NEO Personality Inventory-Revised (Costa and McCrae, 1992) and Harm Avoidance in the Temperament and Character Inventory (TCI; Cloninger et al., 1993). Anxiety-related personality traits are closely associated with depression and anxiety, and are thought to be one of the representative predisposing factors for mood and anxiety disorders (Clark et al., 1994).

On the other hand, a gender difference in the structure and function of the brain has also been pointed out. For example, among structural differences, a higher relative volume of gray matter and a lower volume of white matter and cerebrospinal fluid have been reported in females in comparison with males (Filipek et al., 1994; Gur et al., 1999). As to functional differences, regionally, lower glucose metabolism in the ventromedial aspects of the temporolimbic regions and higher glucose metabolism in the cingulate cortex have been demonstrated in females relative to males, although global glucose metabolism is roughly equivalent (Gur et al., 1995). However, any gender difference in the neurobiological basis of anxiety-related personality traits still remains unclear.

Several functional neuroimaging studies have examined the relationship between the brain and anxiety-related personality traits in healthy subjects in a resting state (Haier, 2004). For example, in a study using single photon emission computed tomography (SPECT), regional cerebral blood flow (rCBF) in the prefrontal gyrus close to the anterior cingulate gyrus (ACC), orbitoinsular junction, parahippocampal gyrus, fusiform gyrus, and inferior temporal gyrus was observed to be negatively correlated with Harm Avoidance (Sugiura et al., 2000). Moreover, several studies using positron emission tomography (PET) have found that anxiety-related personality traits have significant negative relationships with the binding potentials of dopamine D2 receptors in the amygdala (Yasuno et al., 2001) and serotonin 2A receptors in the ACC, in addition to the lateral temporal cortex including the fusiform gyrus (Moresco et al., 2002), the glucose metabolic rate in the insula (Deckersbach et al., 2006), and the glucose metabolic rate in the ACC and lateral temporal cortex (Youn

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doi:10.1016/j.pscychresns.2008.10.002

Table 1
Sex differences in personality traits of the Harm Avoidance and its subscales.

	Males ($n=65$)	Females ($n=37$)	T	df	P^a
Harm Avoidance	48.2±8.0 (34–68)	56.3±9.8 (33–79)	−4.50	100	<0.001
Anticipatory Worry	11.7±2.5 (6–18)	13.6±2.6 (8–19)	−3.66	100	<0.001
Fear of Uncertainty	13.5±2.6 (8–19)	15.7±2.6 (10–20)	−4.18	100	<0.001
Shyness	11.0±2.7 (5–17)	13.2±3.5 (7–20)	−3.53	100	0.001
Fatigability	12.1±2.7 (6–19)	13.7±3.3 (7–20)	−2.70	100	0.008

Mean ± standard deviation (range).
[a] Two-tailed, independent t test for continuous variables.

et al., 2002). Furthermore, in our previous study, which examined the relationship between the TCI and cerebral glucose metabolism (Hakamata et al., 2006), significant negative associations with Harm Avoidance were observed in the ventromedial prefrontal cortex (vmPFC), very close to the orbitofrontal cortex (OFC), middle temporal gyrus, parahippocampal gyrus, and fusiform gyrus (Hakamata et al., 2006). Unfortunately, gender difference was not taken into consideration in these previous studies. Considering that females are known to show higher scores than males for anxiety-related personality traits (Jorm, 1987), it is also likely that females show a more obvious negative association with Harm Avoidance in the vmPFC encompassing the ACC and OFC, the limbic and adjoining regions such as the amygdala, parahippocampal gyrus, and insula, and the lateral temporal cortex.

In the present study, to clarify any gender-related neurobiological difference in the formation of anxiety-related personality, the relationship between Harm Avoidance and brain glucose metabolic rates, focusing especially on those in the vmPFC, limbic system and its adjoining regions, and the lateral temporal cortex, were examined by taking gender effects into consideration using a new large cohort sample.

2. Methods

2.1. Ethical considerations

This study was conducted after obtaining approval from the Ethics Committee of the Nagoya PET Imaging Center. Written informed consent to participate was obtained from all subjects.

2.2. Subjects

The subjects were recruited from a healthy cohort who had been attending Nagoya PET Imaging Center to undergo PET screening for cancer. Those who had been receiving psychiatric or neurological treatments, had abnormal findings in brain magnetic resonance imaging (MRI), or had significant medical illnesses or psychiatric disorders, i.e. past or present history of medical or psychiatric treatment, were excluded from the present study. A total of 102 healthy subjects participated (65 males and 37 females).

2.3. Measurement of anxiety-related personality traits

To measure anxiety-related personality traits, the components of temperament dimensions extracted from the Japanese version of the Temperament and Character Inventory (TCI) (Cloninger et al., 1993), for which the reliability and validity have been established by Kijima et al. (1996), were used. In the TCI, an anxiety-oriented temperament is described as Harm Avoidance. Harm Avoidance is a temperament characterized by behavioral inhibition such as pessimistic worry in anticipation of future problems, passive avoidance behaviors such as fear of uncertainty and shyness of strangers, and rapid fatigability (Cloninger et al., 1993).

2.4. PET/CT procedures

All PET/CT studies were performed using a Discovery LS (GE Healthcare, Ltd., USA). Patients fasted for 6 h before receiving 200 MBq of [^{18}F]fluorodeoxyglucose (^{18}F-FDG, and the uptake period was 40 min. All studies were performed in a dimly lit room with no photic or auditory stimulation. During both the injection and PET scanning, subjects were asked to lie supine with their eyes closed. At the beginning of PET scanning, the subjects were instructed not to engage in any activities. Spiral CT acquisition of the head was performed (0.8 s/rotation; 140 kV; 40 mAs), and immediately after the CT study and without moving the patient, the PET emission scan was started.

2.5. Data analysis

Spatial pre-processing and statistical analysis were performed using Statistical Parametric Mapping (SPM) 2 (Institute of Neurology, University College of London, UK) implemented in Matlab (Mathworks Inc., USA; Friston et al., 1994, 1995a,b, 1996). All reconstructed images were spatially normalized into the Montreal Neurological Institute (MNI, McGill University, CA, USA) standard template to remove any intersubject anatomical variability (Talairach and Tournoux, 1988; Friston et al., 1995a). The MNI coordinates obtained from the results of SPM 2 were converted into the Talairach coordinates using software that was downloaded from the following URL: http://www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml. Affine transformation was performed to determine 12 optimal parameters to register the brain on our original FDG template. Subtle differences between the transformed image and the template were removed by a nonlinear registration method using the weighted sum of the predefined smooth basis functions used in discrete cosine transformation. Spatially normalized images were smoothed by convolution with an isotropic Gaussian kernel with a 12-mm FWHM. The effects of global metabolism were removed by normalizing the count of each

Table 2
Cortical regions showing significant correlations among glucose metabolism and Harm Avoidance in females and males.

Males ($n=65$)							Females ($n=37$)						
Cortical regions (Brodmann's area)[a]	Laterality	Talairach coordinates			k	Z	Cortical regions (Brodmann's area)[a]	Laterality	Talairach coordinates			k	Z
		x	y	z					x	y	z		
Positive correlation with HA							*Positive correlation with HA*						
None							None						
Negative correlation with HA							*Negative correlation with HA*						
None							Superior frontal gyrus	L	−34	58	−11	1866	4.10
							Medial frontal gyrus (BA11)	L	−6	46	−11		
							Medial frontal gyrus (BA11)	L	−10	58	−13		

Abbreviation: BA, Brodmann's area.
[a] Age and other temperament dimension scores were incorporated as nuisance variables.

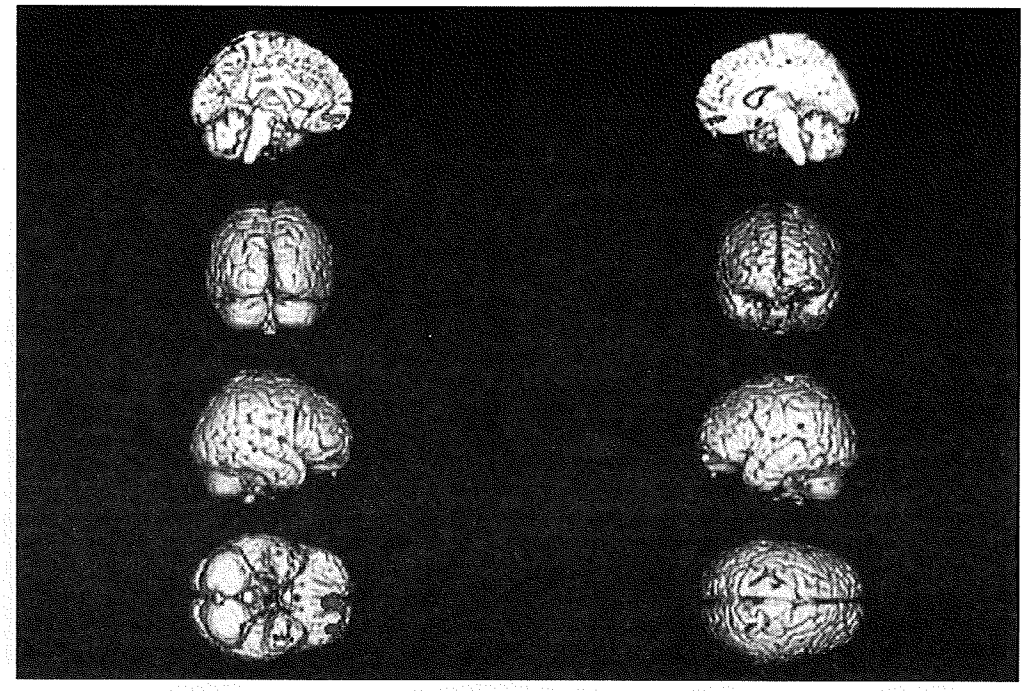

Fig. 1. Significant negative correlation between brain cerebral glucose metabolism and Harm Avoidance in 37 females.

voxel to the total count for the brain (proportional scaling in SPM). After the appropriate design matrix had been specified, the condition of each voxel in each subject was assessed according to the theory of Gaussian fields. The exact level of significance of differences between conditions was characterized by peak amplitude. In the present study we focused on a cluster level to detect significantly different regions, because our sample size was not sufficiently large for random field theory and would therefore lead to type II errors (pseudonegative). To reveal the regions that were significantly correlated with Harm Avoidance, correlation analysis was performed for each voxel on the general linear approach between Harm Avoidance or its subscale scores and glucose metabolism in males, females, and all the subjects individually. In the individual analysis of females or males, age and the scores of three other individual temperament dimensions were incorporated as nuisance variables. In the analysis of the subjects as a whole, gender, age, and the scores of other three individual temperament dimensions were also incorporated as nuisance variables. The resulting SPM $\{t\}$ value was converted to an SPM $\{z\}$ value for Harm Avoidance. The height threshold (u) used to interpret the correlation in terms of probability level was set at $z=3.18$ ($P<0.001$), with each cluster requiring a peak voxel of $z\geq 3.18$ without correction for multiple comparison. The extent threshold (k) was set at 100 voxels, this being sufficient to remove any small noisy clusters that might have reached significance by chance.

Table 3
Cortical regions showing significant correlations among glucose metabolism and Harm Avoidance in the total sample of 102 subjects (females and males).

Cortical regions[a] (Brodmann's area)	Laterality	Talairach coordinates			k	Z
		x	y	z		
Positive correlation						
None						
Negative correlation						
Medial frontal gyrus (BA10)	R	6	40	−9	254	4.58
	R	−6	50	−10		3.24
	R	6	26	−6		3.18

Abbreviation: BA, Brodmann's area.
[a] Age, sex, and other temperament dimension scores were incorporated as nuisance variables.

3. Results

The mean age of the total 102 subjects was 52.7 (±9.2SD) years (range: 34–73 years). The mean age in the 37 females was 52.6 (±9.4SD) years (range: 34–69 years), and that in the 65 males was 52.8 (±9.2SD) years (range: 36–73 years). There was no significant difference in age between females and males. The sex difference in Harm Avoidance and its subscales is shown in Table 1. Females had significantly higher scores for Harm Avoidance and all of its subscales. Anatomical areas where Harm Avoidance was correlated significantly with glucose metabolism in females and males are shown in Table 2. Harm Avoidance was found to have a significant negative relationship with the anterior portion of the vmPFC encompassing the OFC only in females (Fig. 1). Moreover, when a gender effect was excluded, Harm Avoidance was also found to be negatively correlated with the anterior portion of the vmPFC in the 102 subjects as a whole (Table 3 and Fig. 2). As to the sub-scales of Harm Avoidance, Fatigability was positively correlated with the lentiform nucleus and Anticipatory Worry was negatively correlated with the medial portion of the parietal cortex including the paracentral lobule and precuneus in males, while Fear of Uncertainty was negatively correlated with the parahippocampal gyrus in females (Table 4). In the 102 subjects as a whole, Anticipatory Worry and Shyness were negatively correlated with the medial parietal cortex including the paracentral lobule and/or pecuneus. Fear of Uncertainty was negatively correlated with the lateral temporal cortex. Fatigability was negatively correlated with the lateral occipital cortex, which corresponds to the visual cortex (Table 5). No positive correlation was observed.

4. Discussion

This is the first functional neuroimaging study to have examined the relationship between Harm Avoidance and brain glucose

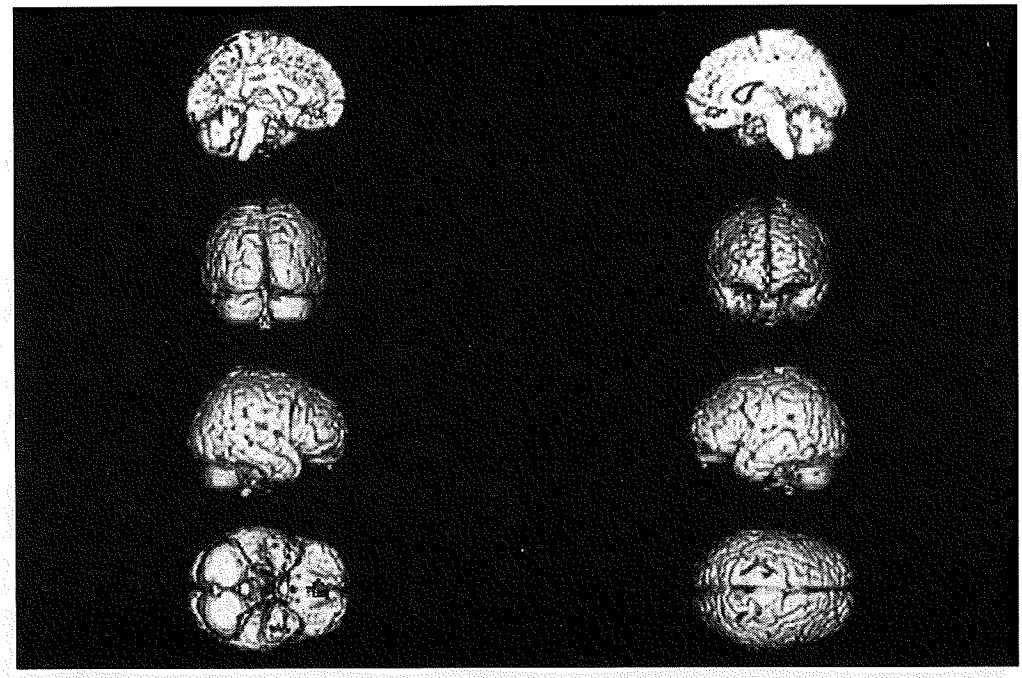

Fig. 2. Significant negative correlation between brain cerebral glucose metabolism and Harm Avoidance in the total sample of 102 subjects (when a gender effect was excluded).

metabolic rates using a large new cohort sample taking gender effect into consideration.

There was a clear gender difference in the results obtained for the 37 females and 65 males; Harm Avoidance was observed to have a significant negative relationship with the anterior portion of the vmPFC encompassing the OFC only in females, and not in males. No other brain regions except for the anterior vmPFC were significantly correlated with Harm Avoidance. A significant negative association between Harm Avoidance and the anterior vmPFC was also observed in our previous study (Hakamata et al., 2006). In other earlier studies, as mentioned above, Harm Avoidance was reported to be negatively correlated with the ACC, the limbic system and its adjoining regions, and the lateral temporal cortex (Deckersbach et al., 2006; Sugiura et al., 2000; Moresco et al., 2002; Youn et al., 2002; Yasuno et al., 2001). As to the ACC and the lateral temporal cortex, we found in the present sample that the glucose metabolic rates in these brain regions had a significant negative relationship with Harm Avoidance when the height threshold was set at $P=0.005$, although no significant cluster remained at $P=0.001$. As to the limbic system and its adjoining regions, however, we did not find any significant differences despite the larger sample size. Given that any brain regions other than the anterior vmPFC disappeared at $P=0.001$, only the anterior vmPFC may be substantially involved in the formation of Harm Avoidance. In addition, interestingly, the anterior portion of the vmPFC, whose cluster corresponds to that found in females, was also found to be negatively correlated with Harm Avoidance in the result for the subjects as a whole, where a gender effect was controlled for. The complete lack of significant association with the anterior vmPFC and

Table 4
Cortical regions showing significant correlations among glucose metabolism and subscales of Harm Avoidance in females and males.

	Males ($n=65$)							Females ($n=37$)						
	Cortical regions (Brodmann's area)[a]	Laterality	Talairach coordinates			k	Z	Cortical regions (Brodmann's area)[a]	Laterality	Talairach coordinates			k	Z
			x	y	z					x	y	z		
Positive correlation														
Anticipatory Worry	None							None						
Fear of Uncertainty	None							None						
Shyness	None							None						
Fatigability	Lentiform nucleus (lateral globus pallidus)	L	−26	−18	−1	171	4.08	None						
	Lentiform nucleus	L	−10	4	−7	153	3.60							
	Anterior cingulate (BA25)	L	0	11	−9		3.35							
Negative correlation														
Anticipatory Worry	Precuneus (BA7)	L	−6	−50	58	1532	4.65	None						
	Paracentral lobule (BA5)	R	4	−44	56		4.44							
	Paracentral lobule (BA31)	R	4	−25	47		4.10							
Fear of Uncertainty	None							Parahippocampal gyrus (BA36)	R	42	−31	−7	101	3.64
Shyness	None							None						
Fatigability	Inferior occipital gyrus (BA19)	L	−42	−76	−6	129	3.69	None						

Abbreviation. BA, Brodmann's area.
[a] Age and other temperament dimension scores were incorporated as nuisance variables.

Table 5
Cortical regions showing significant correlations among glucose metabolism and subscales of Harm Avoidance in 102 subjects (females and males).

	Cortical regions[a] (Brodmann's area)	Laterality	Talairach coordinates			k	Z
			x	y	z		
Positive correlation							
Anticipatory Worry	None						
Fear of Uncertainty	None						
Shyness	None						
Fatigability	None						
Negative correlation							
Anticipatory Worry	Pecuneus (BA7)	L	−6	−49	60	384	4.15
	Paracentral lobule (BA5)	R	6	−42	54		3.65
	Paracentral lobule (BA31)	R	6	−21	47	116	3.81
Fear of Uncertainty	Inferior temporal gyrus (BA20)	R	36	−8	−38	226	4.10
	Superior temporal gyrus (BA38)	R	32	8	−42		3.12
Shyness	Pecuneus (BA7)	R	26	−63	27	132	3.98
Fatigability	Middle occipital gyrus (BA18)	L	−40	−78	−8	131	3.90

Abbreviation. BA, Brodmann's area.
[a] Age, sex, and other temperament dimension scores were incorporated as nuisance variables.

Harm Avoidance in males, despite the larger sample size, suggests that the anterior vmPFC may be commonly involved in Harm Avoidance in both genders, although its involvement tends to be more predominant in females than in males.

As an additional analysis, the relationships between specific aspects of Harm Avoidance and brain glucose metabolism were examined. However, the anterior vmPFC was not observed to be significantly correlated with sub-scores on Harm Avoidance. This implies that the function of the anterior vmPFC is associated not with specific aspects, but with whole aspects of Harm Avoidance. Recent functional neuroimaging studies have revealed that the anterior vmPFC plays an important role in recollection of emotional autobiographical memory mediating integration of sensory information with self-specific information (Levine, 2004; Svodoba et al., 2006). Recollection of autobiographical memory, together with complicated mental processes including self-reflection, emotion, visual imagery, attention, executive functions, and semantic processes, is known to be reflected in the default mode which is active when individuals are not focused on the external environment (Buckner et al., 2008). In the present study as well as previous functional studies, participants' brain activities in a resting state (i.e. lying with the eyes closed but not sleeping) are considered to be a representative state of personality, because such activities are considered to occur from a specific pattern of thoughts or feelings experienced frequently in one's daily life when a subject is not focused on the external environment. Given that a resting state reflects a default mode of the brain (Raichle and Snyder, 2007) and the anterior vmPFC is involved in recollection of emotional autobiographical memory (Levine, 2004; Svodoba et al., 2006), individuals with high Harm Avoidance who have low baseline activity in the anterior vmPFC may show characteristics of a function associated with the default mode, i.e., emotional autobiographical memory recollection. In fact, healthy subjects with a high anxiety-related personality trait have been reported to show reduced autobiographical memory specificity (i.e. overgenerality) (Chan et al., 2007). Overgenerality, and not only Harm Avoidance (Gil and Caspi, 2006), was also shown to be a risk factor for anxiety disorder in a prospective study (Bryant et al., 2007). Moreover, in patients with mood and anxiety disorders, the risk of which is known to be higher in females than in males, the function of the anterior vmPFC has been reported to be altered (Rauch et al., 2006; Steele et al., 2007), and autobiographical memory specificity has been shown to be reduced (Williams and Moulds, 2008; Kleim and Ehlers, 2008). Therefore, hypoactivity of the anterior vmPFC in a resting state may be a risk factor for emotional disorders in individuals with a high anxiety-related personality trait, possibly because it is associated with the specific recollective form of autobiographical memories.

Several limitations should be considered when interpreting the present results. First, the regional glucose metabolism measured in the present study was not an absolute but a relative value because no arterial or venous blood sampling was conducted. Absolute values are also likely to be important when examining the neurobiological basis of personality traits. Second, the concrete function of the anterior vmPFC was not identified because measurement was conducted in a resting state. Third, any dynamic functional relationship between the anterior vmPFC and other regions possibly engaged in Harm Avoidance was not identified in the present study using PET, which has relatively low time resolution. To identify the specific function of the anterior vmPFC and its dynamic functional relationship with other possible brain regions regarding Harm Avoidance, an imaging technique with a higher time resolution should be used, such as functional resonance magnetic imaging (fMRI).

The present study has revealed that individuals who exhibit a higher score for Harm Avoidance have lower glucose metabolic activity in the anterior vmPFC, which has been shown to be involved in the recollection of emotional autobiographical memory, mediating the integration of sensory information with self-specific information, this tendency being evident more clearly in females than in males. The anterior vmPFC may have potential as a neural target for the prevention or therapy of emotional disorders, especially in females.

Acknowledgements

Dr. Yuko Hakamata is a Research Fellow of the Japan Society for the Promotion of Science.

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うつ病の現状

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うつ病は，双極性障害（躁うつ病）とともに気分障害のカテゴリーに含まれる．健康なときにも気分の浮き沈みを経験するが，気分障害は（1）程度が強く，（2）持続期間が長い．つまり，苦しくて生きているのがつらいほどのうつ状態が，気分の入れ替えができないまま一定期間以上持続する．

気分障害は頻度が高く，自殺の原因になったり就労・就学を妨げるなど社会的損失をもたらすため，その対応が重要視されている．また身体疾患を有する患者に気分障害が高率に合併することが知られており，すべての医療従事者が気分障害について理解しておく必要がある．

keyword
大うつ病性障害，大うつ病エピソード，
非定型うつ病，抗うつ薬，認知行動療法

本稿ではうつ病について述べるに留めるが，その病期にうつ病相を含む双極性障害の可能性を常に念頭に置く必要があることは言うまでもない．

疫学

WHO 統合国際診断基準（CIDI）を用いた疫学調査によると，日本における大うつ病性障害の 12 カ月有病率は 3％，生涯有病率は 7％であった．大うつ病性障害の平均発症年齢は 20 歳代半ばで 40 歳までに発症するものが半数を占めるとされるが，わが国では中高年でも頻度が高い．また，女性は男性に比べて 12 カ月有病率，生涯有病率とも約 2 倍である．

成因

気分障害の発症には遺伝的要素と環境的要素の双方が関与する．遺伝的要素の関与が大きい双極性障害と異なり，大うつ病性障害は環境的要素，すなわちストレスになるようなさまざまな出来事や被養育体験（どのように育てられたか）の影響が比較的大きい．しかし病因・病態の分子レベルにおけるメカニズムはいまだ明らかにはなっておらず，仮説に留まっている．

症状

■大うつ病エピソードの基本症状

抑うつ的な気分と，何事についても興味・

表1　大うつ病エピソードの診断基準(DSM-IV-TR：2000)

A. 以下の1～9までの項目のうち，5個以上の項目（1か2のどちらかは必ず含まれる）が，毎日，2週間以上続く
1. 抑うつ気分（ほとんど一日中続く）
2. 興味ないし喜びの著しい喪失（ほとんど一日中続く）
3. 体重あるいは食欲の変化（減少ないし増加）
4. 睡眠障害（不眠もしくは過眠）
5. 無価値観あるいは自責感
6. 自殺念慮（反復して起こる）あるいは自殺企図ないし明確な自殺の計画
7. 疲労感あるいは気力の減退
8. 思考力や集中の減退あるいは決断困難
9. 精神運動性の焦燥(イライラ落ち着かない)もしくは抑制(動きが少ない)
・観察項目:他者の判断によるもので，患者の主観ではない
B. 混合性エピソードの規準を満たさない
C. 症状が，本人に著しい苦痛をもたらか，あるいは対人面，職業面などの機能障害を引き起こしている
D. 乱用薬物や投薬あるいは身体疾患による症状ではない
E. 死別反応では十分に説明されない．すなわち，症状が2カ月を超える，あるいは症状の程度が激しい

関心や楽しさが感じられなくなってしまうことである．大うつ病エピソードの診断基準(表1)では，症状の数(2つの基本症状のうち1つは必ず存在したうえで，他の症状と合わせて5つ以上）と症状の持続期間（2週間以上にわたってほぼ毎日続くこと）が求められている．

診断基準には取り上げられていないが，不安は多くのうつ病性障害患者が示す症状である．また性欲減退，身体の痛み，発汗，便秘などの自律神経症状をともなうことも多い．

日内変動はうつ病においてしばしば認められる．「朝にもっとも調子が悪く，夕方以降になると少し楽になる」といったパターンを示すことが多い．

大うつ病性障害患者は，抑うつ気分，無価値感，自責感が生じるが，その背景には自分自身や自分の置かれている状態を過度に悲観的にとらえていることが多い．この大うつ病性障害に見られる否定的なとらえ方の延長線上にある妄想をDSM*では「気分に一致した精神病症状」と称する．「取り返しのつかない過ちを犯した」などの罪業妄想，「不治の病にかかっていて助からない」といった心気妄想，「家に金がないので入院できない(事実ではない)」などの貧困妄想が代表であり，これらをまとめて微小妄想と呼ぶ．また一切の存在(身体，人格，外界）を否定する否定妄想（コタール症候群）を呈することもある．

診断・分類

DSM-IV-TRにおいて，気分障害の患者はうつ病性障害，双極性障害，その他の気分障害に大別される(表2)．うつ病性障害の診断に際しては，まず身体疾患や薬物によって症状が引き起こされている可能性を除外することが必須である．その後に躁病エピソード，軽躁病エピソード，混合性エピソードの有無を確認し，双極性障害の可能性についても除

*DSMとは米国精神医学会の診断基準[6]である．現在はDSM-IV-TRが用いられている．

表2　気分エピソードと気分障害の分類(DSM-IV-TR：2000)

気分エピソードの分類		気分障害の分類	
大うつ病エピソード		うつ病性障害	大うつ病性障害
躁病エピソード	開放的になる，あるいは怒りっぽくなる状態の，程度が異常に強く，かつその状態が1週間以上持続する．普段のその人の姿とは明らかに異なっている．		気分変調性障害
		双極性障害	双極I型障害
			双極II型障害
軽躁病エピソード	躁病エピソードと症状項目は同じだが，期間・程度が軽いものである．	その他	気分循環性障害
			一般身体疾患による
混合性エピソード	うつ病の症状と躁病の症状が入り混じって出現する状態である．		物質誘発性

表3　大うつ病性障害の診断基準(DSM-IV-TR：2000)

A. 1回以上の大うつ病エピソードが存在
B. 大うつ病エピソードの症状が，統合失調感情障害によるものではなく，統合失調症，失調様障害，妄想性障害などの精神病性障害が合併はしない
C. 過去に，躁病エピソード，混合性エピソード，軽躁病エピソードが存在しない

表4　気分変調性障害の診断基準(DSM-IV-TR：2000)

A. 抑うつ気分がほとんど一日中存在し，それのない日よりもある日のほうが多く，患者自身の言明または他者の観察によって示され，少なくとも2年間続いている
B. 抑うつの間，以下のうち2つ以上が存在する
(1)食欲減退，または過食
(2)不眠，または過眠
(3)気力の低下，または疲労
(4)自尊心の低下
(5)集中力低下，または決断困難
(6)絶望感
C. この障害の2年の期間中，一度に2カ月を超えてAおよびBの症状がなかったことはない
D. 大うつ病エピソードを満たさない

外する．

うつ病性障害は以下の2つに分類される．

大うつ病性障害（表3）

1回以上の大うつ病エピソードがあることが基本である．精神病性障害や双極性障害を除外する必要がある．

気分変調性障害（表4）

2年以上の期間にわたり抑うつ気分のある日が多く，しかし抑うつ気分が大うつ病エピソードに至らない状態である．

参考：一般身体疾患による気分障害と物質誘発性気分障害（表5）

さまざまな身体疾患や物質による直接的な生理作用の結果，顕著かつ持続的な気分の障害をきたす場合である．臨床上では最初に鑑別診断すべき区分である．とくに高齢者が気分エピソードの症状を呈した場合は，一般身体疾患または物質によって引き起こされた気分障害との鑑別がとりわけ重要である．

■臨床的特徴について

同じ気分エピソードであっても，特有の症状の出現する場合や一定の時期に現われるといった臨床的特徴を持つ場合がある．DSM-IV-TRでは臨床的特徴を特定するための用語が用意されている（表6）．

メランコリー型

大うつ病エピソードについて使用される．「すべての活動に関する興味・喜びの消失」あるいは「通常快適に感じられる刺激に対する反応の消失」が存在することが前提であり，