genetic correlations among them. When subscales defining the same personality traits are phenotypically correlated with each other, the correlation may be due to genetic influence, environmental influence, or both. Thus, items or subscales defining the same trait may not share their etiology: some correlations among them may be due to genetic influences, whereas other correlations may be due to environmental influences. In fact, Ando et al. (2004) showed that a subscale of Novelty Seeking was genetically correlated to a greater extent with subscales of Harm Avoidance than with the other Novelty Seeking subscales. Although no one could predict the results beforehand, this genetic heterogeneity may be one of the reasons for the many inconsistent results of molecular genetic studies that examined the relationships between the DRD4 polymorphism and novelty seeking (Munafo et al., 2003). As such, computing genetic correlations and excluding genetically unrelated subscales or items makes genetically crisp categories (Faraone et al., 1999) and helps the association study by increasing the statistical power. Considering the fact that Cloninger's model is one of most accepted biological models of temperament, any temperamental traits that are theorized to have a specific genetic basis need to be empirically tested for genetic consistency before a molecular genetic study is conducted.

In this paper, we applied this approach to effortful control (EC), a temperament proposed by Rothbart et al. (2000). EC is a unique concept since it captures a self-regulative process that is rarely modeled by other personality theorists. EC is defined as 'the ability to inhibit a dominant response to perform a subdominant response' (Rothbart & Bates, 1998, p. 137) or the 'efficiency of executive attention, including the ability to inhibit a dominant response and/or to activate a subdominant response, to plan, and to detect errors' (Rothbart, personal communication, January 26, 2002, cited in Eisenberg et al., 2004). EC can be measured by questionnaires for various age groups ranging from infancy (3 to 12 months old; Rothbart, 1981), preschool and early school years (3 to 7 years old; Rothbart et al., 2001), early adolescence (9 to 15 years old; Ellis et al., 2004) to adulthood (Rothbart et al., 2000).

The reason why the genetic coherency of EC should be empirically tested is its importance in explaining psychopathology. As EC is in essence a measure of executive functioning, and as many experimental studies have shown that the lack of executive attention is found for various forms of psychopathology (Dobson & Dozois, 2004; Gotlib & Cane, 1987; Homack & Riccio, 2004; Mathews & Macleod, 1985; Sharma et al., 2001; Smith & Waterman, 2003), it is predicted that low EC should also be associated with them. In fact, empirical studies have shown that low EC is associated with both externalizing problems and internalizing problems (Eisenberg et al., 2001; Lemery et al., 2002; Oldehinkel et al., 2004). These findings suggest that low EC may be a common diathesis of both types of problems and explain high comorbidity between them. However, it could be also possible that EC consists of genetically heterogeneous subscales, and this heterogeneity enabled the scale to be associated with both externalizing and internalizing problems. In fact, a subscale of EC assessing control of inhibition tends to be associated more with externalizing problems, whereas another subscale assessing control of attention tends to be associated more with internalizing problems (Eisenberg et al., 2001). These two possibilities have very different implications for the field. If EC was shown to be genetically homogeneous, then the molecular genetic basis of EC should be rigorously examined as it can find the genetic risk factor common to both types of problems. Alternatively, if EC was shown to be genetically heterogeneous, then the reason for comorbidity between externalizing and internalizing problems should be explored elsewhere.

Thus, the current study was purported to examine whether EC is influenced by a homogeneous set of genes using Japanese adolescent and adult twin samples. This was done by first conducting univariate genetic analyses to show genetic influences on EC and its subscales, and then computing genetic and environmental correlations between the subscales.

Method

Participants

The questionnaire booklets were mailed to approximately 600 pairs of twins. All participants were volunteers in the Keio Twin Project (Ando & Ono, 1998), recruited via invitations sent to a population-based twin residential list of Tokyo and its neighboring cities. All subjects received written explanations of the purpose of the study, the research items, protection of their privacy, and their right to cancel their participation at any time if they wished. Subjects completed an informed consent agreement document. Subjects under 20 years of age were also required to obtain their parents' written consent. The final sample consisted of 225 pairs of twins, including 152 pairs of monozygotic (MZ) twins (104 female pairs and 48 male pairs) and 73 pairs of dizygotic (DZ) twins (34 female pairs, 16 male pairs and 23 opposite-sex pairs). The age range of the sample was 17 to 32 years (mean age = 24.15, SD = 4.28). Zygosity was determined using the questionnaire developed by Ooki et al. (1990). For a number of pairs, a clear zygosity diagnosis could not be made and their zygosity was determined on the basis of two gene polymorphisms (DRD4 and 5-HTTLPR) and genetic fingerprinting data. The accuracy of zygosity diagnosis is estimated to be between 91% and 95% in the present sample.

Instruments

The instrument used in the present study is the Japanese version of the Effortful Control scale

(Yamagata et al., in press). The EC scale for adults consists of three subscales: Activation Control (ACC), Attentional Control (ATC), and Inhibitory Control (IC). ACC measures the capacity to perform an action when there is a strong tendency to avoid it (e.g., 'I can make myself work on a difficult task even when I don't feel like trying'). ATC measures the capacity to focus attention as well as shift attention when desired (e.g., 'When interrupted or distracted, I usually can easily shift my attention back to whatever I was doing before'). Inhibitory Control measures capacity to suppress inappropriate approach behavior (e.g., 'When I decide to quit a habitual behavioral pattern that I believe to be undesirable, I am usually successful').

The Japanese version was developed through a back-translation procedure of the 35 original items of the Effortful Control scale included in the Adult Temperament Questionnaire (Rothbart et al., 2000). The Japanese version was reported to have good internal consistency (Cronbach's alpha = .90; for subscales, .74 to .84), test–retest reliability (r = .88; for subscales, r = .79 to .89; 3 weeks), and validity (positively correlate with the performance of the Stroop color-word interference task). Participants were asked to fill out the questionnaire with the instruction not to discuss or show their answers to their twin sibling.

Statistical Analysis

In order to assess the genetic and environmental contribution to phenotypic variations of EC and its subtraits, univariate genetic analyses, as described in Neale and Cardon (1992), were conducted with the computer program Mx (Neale et al., 1999). Univariate genetic analysis decomposes the similarities (covariances) of MZ and DZ twin pairs into estimates of additive genetic (A), nonadditive genetic (D), shared environmental (C) and nonshared environmental (E) influences. The effect of additive genetic factors (A) is assumed to be the sum of multiple genes (polygene) whose effects are small and additive to form a quantitative phenotype. The effect of nonadditive genetic factors (D) is assumed to be an interactive (nonadditive) contribution of alleles within a single locus (dominance). Shared environment (C) is the effect that makes family members alike not from heredity but from the common environment shared by all family members. Nonshared environment (E) is the effect that makes family members different even if they live together, such as physical illness and differential parental treatment. It also includes measurement errors.

In order to reveal which factors significantly contribute to phenotypic variances, four models were systematically compared in terms of goodness-of-fit statistics. These are the ACE model in which phenotypic covariances are explained by A, C and E; the ADE model explained by A, D and E; the AE model explained by just A and E; and the CE model explained by just C and E. Akaike's Information Criteria (AIC) was computed and used to determine the best model from these four. The AIC reflects a model's goodness of fit as well as its parsimony, and the model that results in the smallest AIC is regarded as the best. Parameter estimates for A, D, C and E are squared to compute the familiar proportions of the variance symbolized as h^2, d^2, c^2 and e^2.

Table 1

The Mean, SD, Range, and Intraclass Correlations of EC and Its Subscales

					Intraclass correlation	
	M	*SD*	Min.	Max.	MZ	DZ
EC	93.8	13.9	51	130	.45	.21
ACC	33.3	5.9	16	48	.38	.17
ATC	29.5	6.0	12	47	.42	.20
IC	31.0	4.9	14	44	.30	.12

Note: MZ = monozygotic twins; DZ = dizygotic twins; EC = Effortful Control; ACC = Activation Control, ATC = Attentional Control, IC = Inhibitory Control.

In order to compute the genetic and environmental correlations among EC subscales, multivariate genetic analyses were conducted. Multivariate genetic analysis is a model-fitting method to reveal genetic and environmental sources of phenotypic correlations. We first subjected the MZ and DZ within-pair covariances to a Cholesky decomposition using the Mx program as described in Neale and Cardon (1992). Specifically, we fit the AE Cholesky model to the twin covariances to estimate the additive genetic and nonshared environmental covariance matrices. We then converted the parameter estimates to the additive genetic (r_G) and nonshared environmental (r_E) correlations. For example, r_G between variables i and j was calculated from the genetic covariance between i and j (a_{ij}) and the genetic variance of i (a_{ii}) and j (a_{jj}) as such:

$$rG_{ij} = \frac{a_{ij}}{\sqrt{a_{ij} \times a_{jj}}}$$

The genetic and environmental correlations can be interpreted in the same way as any correlation coefficient: they vary from –1.0 to +1.0 to reflect the degree to which two variables are influenced by the same genetic or environmental factors.

Results

Descriptive Statistics

The mean, *SD*, range, and intraclass correlations for both MZ and DZ twins for EC and each of its subscales are shown in Table 1. For total EC as well as its subscales, intraclass correlations for MZ twins were higher than those of DZ twins, suggesting the existence of additive genetic influences.

Univariate Analysis

Table 2 shows the results of univariate genetic analyses of EC and its subscales. In terms of AIC, the AE model fit best for EC as well as its subscales. For the best-fitting AE model, additive genetic effects (h^2) explained 47% of phenotypic variance, whereas non-

Table 2

Results of Univariate Analyses

	model	χ^2	*df*	*p*	AIC	h^2	d^2	c^2	e^2
EC	CE	16.91	4	.00	8.91				
	ACE	8.93	3	.03	2.93				
	AE	8.93	4	.06	0.93	.49	—	—	.51
	ADE	8.42	3	.04	2.42				
ACC	CE	6.81	4	.15	−1.19				
	ACE	2.95	3	.40	−3.05				
	AE	2.95	4	.57	−5.05	.39	—	—	.61
	ADE	2.79	3	.43	−3.21				
ATC	CE	12.59	4	.01	4.59				
	ACE	6.65	3	.08	0.65				
	AE	6.65	4	.16	−1.36	.45	—	—	.55
	ADE	6.36	3	.10	0.36				
IC	CE	10.47	4	.03	2.47				
	ACE	7.18	3	.07	1.18				
	AE	7.18	4	.13	−0.82	.32	—	—	.68
	ADE	6.71	3	.08	0.71				

shared environmental effects (e^2) explained 53% of the variance. With regard to the subscales, heritability estimates ranged from .31 (Inhibitory Control) to .44 (Attentional Control).

Multivariate Analysis

Table 3 shows the genetic and environmental correlations among EC subscales. Correlations among the subscales were all positive in both the genetic and the environmental matrices. Genetic correlations were especially strong, with r_G ranging from .64 for between Activation Control and Inhibitory Control, to .93 for between Attentional Control and Inhibitory Control.

Discussion

This study examined the genetic and environmental etiology of EC using a Japanese adolescent and adult sample. Results of univariate analysis confirmed that EC as well as its subscales had a genetic basis. It is consistent with the finding of Goldsmith et al. (1997) that EC is heritable in childhood (h^2 = 58%). However, it is not surprising given the well-known fact that in adulthood, additive genetic and nonshared environmental effects account for variability in most personality traits (Bouchard & Loehlin, 2001).

The main focus of this study was rather on the genetic relationship between subscales of EC. As Ando et al. (2004) have recently shown in the case of Novelty Seeking, many temperaments were theorized for their genetic basis, but were in need of empirical examination for their genetic coherency. This was also the case for EC, but the multivariate analysis results in this study showed that subscales of EC were genetically correlated to a substantial degree. This suggests that individual differences in control with regard to activating and inhibiting behavior and attention are influenced by the same set of genes and form 'genetically crisp categories' (Faraone et al., 1999). Thus the EC scale can be readily used for the search of its molecular genetic basis. It also suggests that low EC is associated with both externalizing and internalizing problems because low EC can work as a common diathesis for the two types of problems, not because the scale contains genetic noise. Thus the molecular genetic study of EC is fruitful because it may reveal common genetic risk factors for internalizing and externalizing problems and contribute to their prevention.

Initially, the polymorphism of dopamine receptors and that of monoamine oxidase A (MAOA) may be good candidates. Derryberry and Rothbart (1997) and Rueda et al. (2004) proposed that individual differences in EC were founded on the activities of the anterior attentional system consisting of the anterior cingulate gyrus and the lateral prefrontal cortex that are modulated by dopamine. In fact, several neuroimaging studies revealed that tasks that require control of attention activate the anterior attentional

Table 3

Genetic and Environmental Correlations Among EC Subscales

	ACC	ATC	IC
ACC	—	.49	.34
ATC	.71	—	.31
IC	.64	.93	—

Note: Below diagonal: genetic correlations; above diagonal: environmental correlations.

network (Fan, Flombaum et al., 2003; Leung et al., 2000; Rubia et al., 2001), and that the amount of neural activation in anterior cingulate while the subjects performed the task was heritable (Fan et al., 2001) and associated with polymorphisms of the dopamine receptor gene and the MAOA gene (Fan, Fossella et al., 2003).

Testing genotype and environment (G × E) interaction in the development of EC is another direction for future research. Recently, Caspi et al. (2002) showed that aggressive behavior and conduct problems, which are closely related to low EC (Eisenberg et al., 2000; Ellis et al., 2004) were explained by the interaction between a polymorphism of the MAOA gene and parental maltreatment. It could be possible that this interaction accounts for individual differences in EC, and EC mediates the relationship between the G × E interaction and aggressive behavior.

Finally, some methodological limitations should be noted. First, it is unclear whether the present results can be applied to cultures outside Japan. Rothbart et al. (2001) reported that in children, the structure of EC differed in China, Japan and the United States. Thus, in cultures other than Japan, the etiology of EC in adulthood may be different. Further, the sample size of the present study was not sufficient to examine gender-specific effects. Olson et al. (1990) reported that the relationship between behavioral measures of EC and parenting differs depending on gender. Hence, it is necessary to examine gender-specific effects using a larger sample.

In conclusion, the results of the present study indicate that EC is genetically influenced to a substantial degree and has a genetically coherent structure. These results support the validity of the construct from a genetic point of view and encourage the search for a molecular genetic basis of temperament as a common diathesis for both internalizing and externalizing problems.

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Neuroanatomy in monozygotic twins with Asperger disorder discordant for comorbid depression

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Significant genetic contributions to autism spectrum disorders (ASDs) have been reported.[1] However, specific genetic variants that contribute to ASD have not been conclusively identified. Recently, interest has centered on an approach aimed at identifying potential intermediate phenotypes such as neuroanatomic abnormalities, as such findings may facilitate the endeavor to localize specific genetic variants.[2] Here we report common and distinct neuroanatomic abnormalities of a pair of monozygotic twins concordant for Asperger disorder (ASP) but discordant for psychiatric comorbidity. The current study applied individual whole-brain voxel-based morphometry (VBM) to quantitatively identify neuroanatomic abnormalities.

Participants. A pair of 22-year-old male twins with ASP was recruited from the Department of Neuropsychiatry, Hospital of Tokyo University, Japan (see table E-1 on the *Neurology* Web site at www.neurology.org). Diagnosis of ASP was determined for each patient according to the Diagnostic and Statistical Manual for Mental Disorders-IV (DSM-IV) (reference E-1) and further confirmed according to the International Classification of Diseases-10 (reference E-2) criteria through a consensus of two trained child psychiatrists. DNA fingerprint probes were used to establish zygosity, using an eight-probe single-locus DNA profile. DNA testing was performed to rule out fragile X syndrome. Although both the twins showed normal intelligence, one of them had current major depression as a psychiatric comorbidity (for detailed clinical characteristics of each twin, see table E-1). Eighty-two Japanese men without neuropsychiatric disorder served as a comparison sample (mean [SD] age = 28.9 [4.0] years, range 22 to 39 years). The participants were interviewed by trained psychiatrists and screened for the presence or absence of DSM-IV axis I disorder (reference E-3). All subjects were right-handed based on the Edinburgh Inventory (reference E-4). The Ethical Committee of the Faculty of Medicine, University of Tokyo, approved of this study. After a complete explanation, written informed consent was obtained from all participants.

MRI acquisition and analysis. The methods of MRI acquisition and image processing have been described in detail elsewhere.[3] In brief, the MRI data with 0.9375 × 0.9375 × 1.5–mm voxels were obtained from all subjects using a 1.5 T scanner. Processing of the acquired images was similar to that described in our previous study[3] except that, rather than SPM99, the current study employed SPM2, which includes spatial normalization using study-specific customized template, tissue segmentation with extracting nonbrain voxels and smoothing with 12-mm full width at half-maximum. Furthermore, global gray matter, white matter, and CSF volumes were calculated from the optimized VBM procedure.[4] Statistical comparisons of the processed images between the twin pair (n = 2) and controls (n = 82) and between each twin (n = 1) and controls (n = 82) were performed using an analysis-of-covariance model with age and intracranial volumes as confounding covariates. For individual VBM, a statistical analysis method similar to that of a previous study[5] was employed. Significance levels were set at corrected $p < 0.05$.

Results. Significantly reduced gray matter voxel densities were found in the left superior temporal gyrus including superior temporal sulcus (STS), left fusiform gyrus, right amygdala, and right prefrontal cortex (PFC) in twins with ASP as compared with control subjects. Individual VBM revealed reduced gray matter densities in the left STS, fusiform, and right PFC commonly in both twins. In contrast, the reduced gray matter densities in the right amygdala were evident in the twin with comorbid depression but not in the co-twin without mood disorder. No significant group difference in voxel density was detected for other gray matter regions or any of the white matter regions (figure, page 492).

Discussion. Both of the monozygotic twins concordant for ASP had significantly smaller than normal left STS, left fusiform gyrus, and right PFC, regions important for social cognition and behavior (reference E-5). The current findings are generally consistent with previous structural MRI studies in persons with ASD, although some inconsistencies exist in the literature.[6] These findings further suggest a contribution of shared genetic factors to underlying the structural abnormalities in ASD. Of particular interest, however, reduction of the amygdala was evident only in the twin with comorbid depression. Here the difference in age distribution between the twins and the control group and the medication effect on the depressed twin should be considered. Taking into account the age-associated decrease in brain volume[4] and neurotrophic effects of lithium and antidepressants, (reference E-6) however, the elimination of these effects would likely only strengthen the statistical difference. Taken together with the amygdala volume reduction reported in some forms of depression and anxiety (reference E-7), our results have an important implication for the interpretation of structural abnormality of amygdala, which has been extensively demonstrated in adults with ASD (reference E-8). Our results are also in accordance with recent animal studies[7] suggesting a role of the amygdala in abnormal fear and anxiety rather than abnormal social behavior in ASD.

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the August 9 issue to find the title link for this article.

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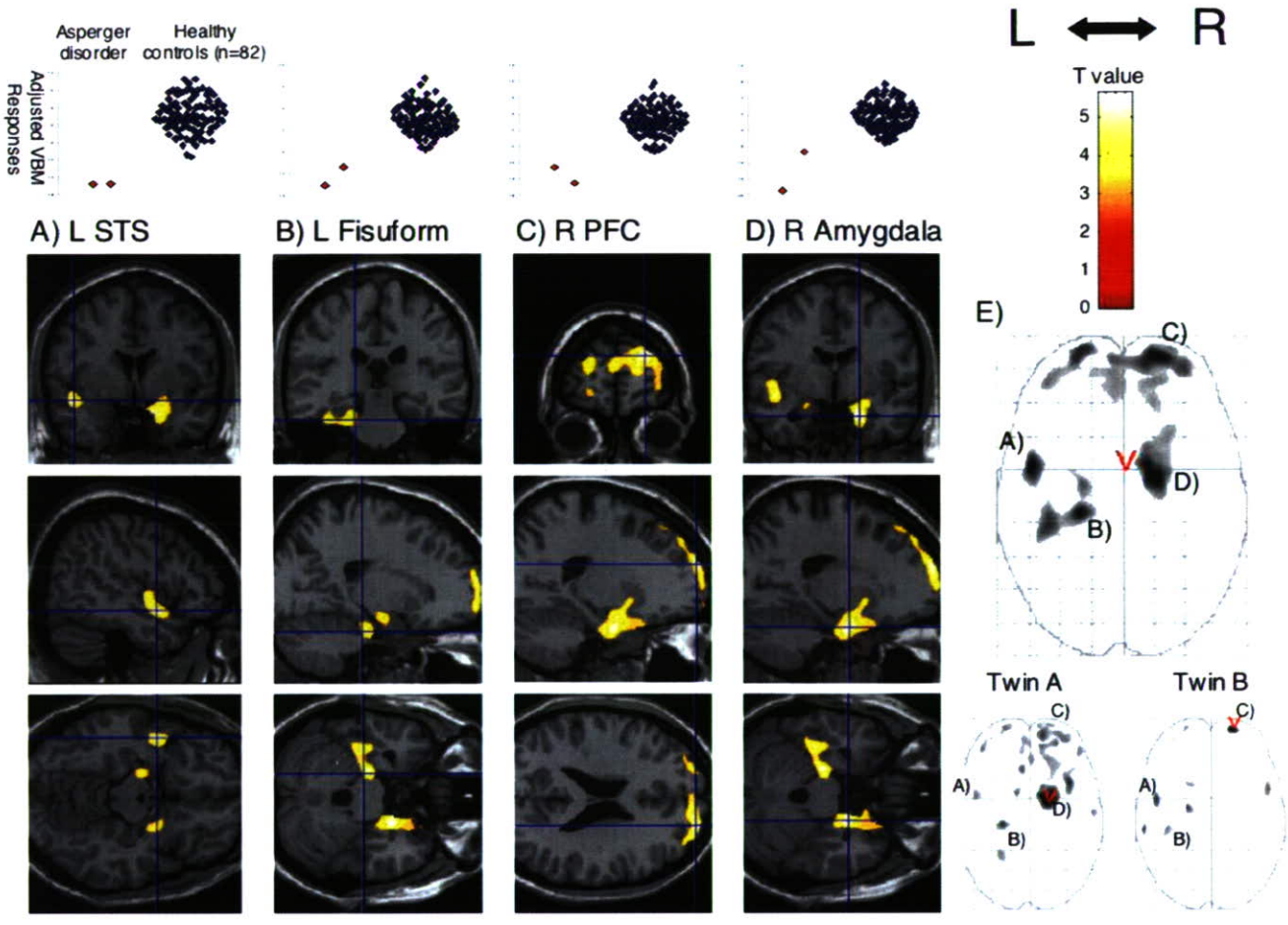

Figure. Morphological abnormalities in twins with Asperger disorder. (Left bottom, A through D) Gray matter voxels with reduced density in the twins with Asperger disorder as compared with normal control subjects (n = 2 vs n = 82) were rendered onto orthogonal slices of the normal template MR images. Voxel threshold: uncorrected p< 0.001; significantly abnormal regions: left superior temporal gyrus including superior temporal sulcus (A): peak coordinate at (x, y, z): (−49, 2, -13), spatial extent k = 1,934, Z(2,81) = 4.94, corrected p = 0.015; left fusiform gyrus (B): (−23, −23, −26), Z = 4.97, k = 3,590, corrected p = 0.013; right prefrontal cortex (C): (20, 61, 23), Z = 5.01, k = 9,617, corrected p = 0.011; right amygdala (D): (18, -3, -26), Z = 5.14, k = 6,514, corrected p = 0.006. (Left top, A through D) Plots of adjusted voxel-based morphometry responses at each brain region. (E) Statistical parametric maps in the axial projection showing gray matter voxels with reduced density in the twins (n = 2; upper map) and each twin (lower maps) as compared with normal controls (n = 82). A significant reduction in the right amygdala (D) found in Twin A was absent in Twin B. Voxel threshold: uncorrected p< 0.001.

A patient with left ventricular thrombus and recurrent stereotypic TIAs

Christine M. Bower, MD; Lola Morgan, MD; and Bruce Ovbiagele, MD

Stereotyped TIAs are presumed to occur secondary to a fixed flow-limiting stenosis of medium/large vessels in the cervicocephalic arterial tree[1] or in situ disease of small deep penetrating arteries in the brain.[2] We report the unusual case of a patient with recurrent stereotypic TIAs associated with the presence of a left ventricular thrombus and with delayed focal ischemia on the T1-weighted MRI sequence.

Case report. A 60-year-old nonsmoking Filipino man, with an unremarkable medical history, reported three distinct episodes of sudden-onset right-sided weakness and numbness and difficulty with expression. These episodes occurred every 2 hours over a 6-hour period. The first two spells lasted 10 minutes, and the third spell lasted 20 minutes.

On admission, his blood pressure was 155/90 mm Hg and pulse was 61 beats/min. Otherwise, general and neurologic exams were normal. Brain CT showed no evidence of infarct. Because of the temporal and stereotypic nature of his spells, we felt that the patient had a fixed flow-limiting stenosis in his left internal carotid or middle cerebral arteries causing hemodynamic compromise. The patient was admitted to the intensive care unit and placed on a heparin drip. MRI of the brain showed a mild hyperintensity on diffusion-weighted imaging (DWI) with corresponding apparent diffusion coefficient hypointensity in the left head and body of the caudate and a portion of the anterior internal capsule (figure, A and B). There was no corresponding signal change on T1-weighted, T2-weighted, or fluid-attenuated inversion recovery images. MR angiograms of the neck and circle of Willis were within normal limits (see the figure, C and D). Despite his stereo-

特集：第28回日本生物学的精神医学会シンポジウム（1）

1-7

シンポジウム：不安障害の生物学ー最前線

パニック障害の遺伝子探索

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Key words：panic disorder, cormordity, NIRS, catecol-O-methyl-transferase, monoamine oxidase A

1．はじめに

パニック障害は動悸，発汗，胸部不快感，めまい感など自律神経系の異常を中心とする複数の身体的な症状を伴いつつ予期しない不安発作が繰り返されることを特徴とする（American Psychiatric Association, 1994）。パニック障害はしばしば慢性の経過を辿り，寛解と増悪を繰り返し，恐怖症や大うつ病など他の精神疾患に合併することも多い（Weissman, et al. 1997）。パニック障害の苦悩は深刻であり，医療への希求は強く，疾患の解明への当事者からの期待と要望は極めて強い。パニック障害は自殺企図が高頻度，救急受診が高頻度などの特徴があり，不安障害全体の直接治療費総額は，統合失調症とほぼ同額とされ，さらに，不安障害による生産性の低下と損失は，直接医療費と同規模の額と推計されている。以上のような観点からパニック障害を解明し，より良い治療に結びつける試みについては，本疾患の患者の苦痛の軽減など医療的な必要性のみならず，医療経済学観点からも社会的な意義が認められるものである。

2．パニック障害における遺伝学的研究の意義について

パニック障害など精神疾患は多因子が複雑に関与する疾患という特徴がある。そのゲノム研究とは形質を説明するゲノム情報を探る研究であり，その研究においては，①合理的な必要性，②適切な形質の定義，③稠密なDNA多型・変異マーカーと，④十分なサンプル数が必要であり，⑤核内遺伝子配列情報が否定される場合にも対応できる方法論（epigeneticsなど）を持つことが重要である。また，パニック障害を研究対象とする合理的必然性ついては，①遺伝因の関与，②表現型が簡潔・明瞭で妥当性を持つこと，③当事者の熱烈な要望があり，協力を得られやすいこと，④医療経費が膨大（罹患率2％程度，救急受診多い）であること，⑤十分なサンプル数を用いた研究が少な

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いことや民族差の存在すること，⑥日本にパニック障害ゲノム研究に有利な条件があることがあげられる。

1．遺伝因子の関与について

以前より不安障害の家系研究において，家族集積性が認められることから遺伝的因子が関係していると推定されていた。パニック障害においても複数の家系研究がなされ，Crowe らはパニック障害患者の直系の子孫では第一度親族中の患者の割合は 17.3％であるのに比べ，正常対照群では約 1.8％と発病のリスクが高まる傾向を指摘している（Crowe et al., 1983）。その他，米国やベルギー，オーストラリアなどで行われた大規模調査において患者群の第 1 親等では対照群と比較して 8 倍の危険率になっている（Knowles, JA. & Weissman, MM, 1995）。Goldstein らによる発症年齢における研究では，20 歳以前の発症では家族性が強く 17 倍のリスクがあるのに対し，20 歳以後の発症では 6 倍のリスクであった（Goldstein et al., 1997）。親子間の発症年齢の差を見た研究でも，親の平均発症年齢が約 30.1 歳，子供では 20.8 歳であったが，評価のタイミングなどの要因がバイアスとなっているため表現促進効果（anticipation）については一概には評価できない状況である（Heiman et al., 1996）。双生児研究でも一卵性双生児の方が二卵性に比較して一致率が高くなっており（Torgersen, 1983），Kendler らの女児を用いた研究によると，一致率は一卵性 24％に対して二卵性は 11％であった（Kendler et al., 1992）。最近の双生児研究では全般性不安障害についての遺伝率は 32％に対して，パニック障害の遺伝率は約 48％と報告されている（Hettema et al., 2001）。以上をまとめると，パニック障害の遺伝的因子の関与についての疫学的な知見については第一度親族の罹患危険率が有意に高いこと，同胞相対危険が高いこと，双生児研究での一致率や遺伝率の高さがあげられる。

2．パニック障害の表現型について

パニック障害の表現系として呼吸器症状，自律神経症状，循環器症状があり，その表現型が簡潔・明瞭で妥当性があることを特徴としている。その主要症候は予期できないパニック発作，その反復・それに続く予期不安；高頻度の空間恐怖，抑うつの合併がある。また，パニック発作＝簡潔明瞭な症候をもち，短期間の脳機能異常を反映すると考えられ，その他として誘発物質の存在（CO_2，乳酸）や主要症候への SSRI などの治療薬が有効な反応を示すことなどがある。我々は 1000 例以上のパニック障害患者の初発時パニック発作の症状別頻度を検討した（梶木ら, 2005）。その結果として，14 番目までの症状（30％以上の患者に存在）のうち，13 個は国際的精神疾患診断基準の症状と共通，一つ（口渇）は異なり（10 位）で，日本人に特有の民族差と考えられた。また性差（男性＜女性）と発症年齢（青年後期～ 30 代半ば好発）は国際的に共通と判断された。

3．日本特有の条件と研究計画について

今日までのパニック障害の連鎖研究における家系の総数は不十分であり，更に対象家系（患者数）を増やした形での研究が必要とされている。わが国にはパニック障害専門クリニックの存在（関東・東海）という特別な臨床フィールドの存在があり，既に 8,000 人以上が登録され，現在 4,000 人が受診中であり，世界最大と考えられている。これらを対象に既に 500 人以上のサンプリングが行われており，合計 1,000 人のサンプリングを計画している。双生児の発見も既に 5 組となっている。パニック障害は両親の協力も得られやすく，また罹患同胞対が統合失調症よりも発見しやすいという臨床的な印象もあり，短期間のサンプリングを可能にする要素に恵まれている。本研究においては TDT によるゲノムスキャンを先行させ，罹患同胞対による連鎖研究と染色体スクリーニングを併行する計画で進められており，パニック障害に関する疾患感受性遺伝子の解明を目標としている。

3．パニック障害の遺伝学的研究の紹介

1．一卵性双生児不一致例についての検討

一卵性双生児は，遺伝的には全く相等しい二個

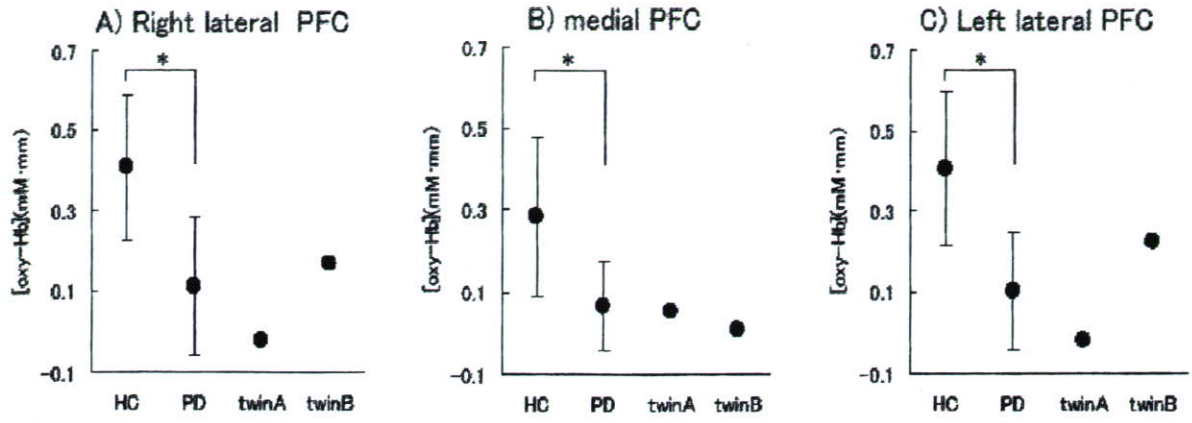

図1　一卵性双生児不一致例のNIRS（前頭葉機能）
Mean［oxy-Hb］changes during the word fluency task
Twin A：パニック障害　Twin B：健常者
＊：NC：normal control, PD：panic disorder　p<0.001 by t-test

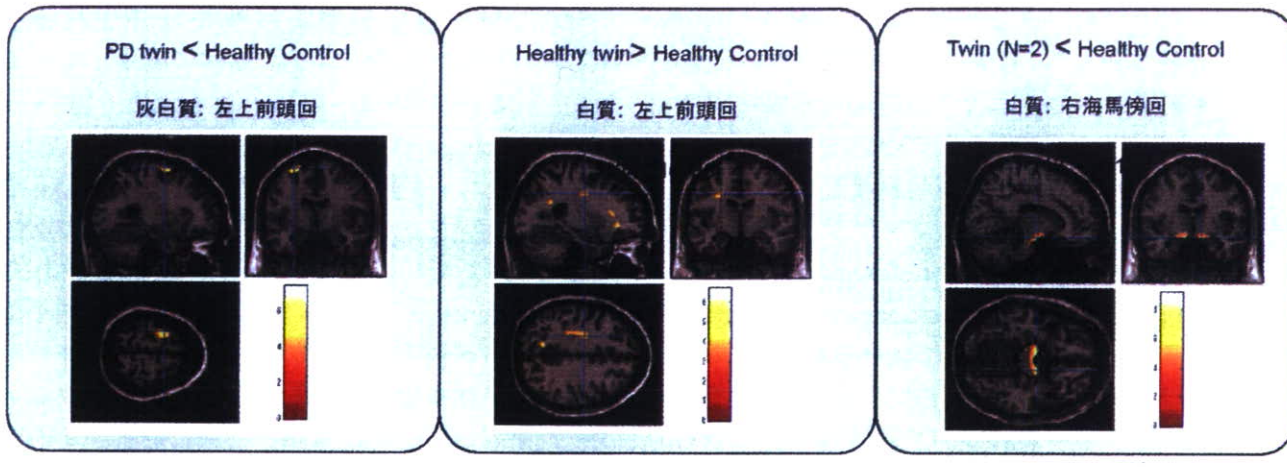

図2　一卵性双生児　パニック障害不一致例におけるVBM法を用いた脳形態画像解析

体であるが，その一方のみがパニック障害を発症している場合，すなわち一卵性双生児不一致例における両者の差異を検討することは疾患の原因を突き止める上で有力なアプローチの方法であるといえる。本研究では，パニック障害一卵性双生児不一致例（30歳男性ペア）についての光トポグラフィーやMRIを用いた検討を行った。両者において，各種心理検査結果については社会不安尺度であるSTAI-S以外には殆ど差を認めなかった。次いで，近赤外線スペクトロスコピー（NIRS）を用いた検討を，ETG-4000･日立メディコ社製の52ch NIRS装置を用いて行った。被験者への検査は語流暢課題を用いた。一卵性双生児不一致例について，課題開始30秒後のoxy-Hbの変化は**図1**に示した（Twin A: パニック障害，Twin B：健常者）。これらの結果からパニック障害における前頭葉機能（特に内側部）の低下が示唆された。次いで，MRIを施行し，一卵性双生児不一致例におけるVBM法を用いた脳形態画像解析を行った。ここで，パニック障害罹患者（A）では，健常男性群20名と比較して，左上前頭回灰白質の萎縮が認められたが，健常者（B）では，逆に左上前頭回白質において，健常男性群20名より大きかった。また双生児ペア（2名）と健常男性群20

名を比較した結果では，右海馬傍回を中心とした領域で萎縮が認められた。以上の結果はパニック障害患者における海馬傍回を含む辺縁系の変化については疾患感受性などの脆弱性を示し，パニック障害の発症に関与するのは前頭葉であるという可能性を示唆するものであった。

2．家族歴の有無による検討

100例以上のパニック障害患者に対する近赤外線スペクトロスコピーによる検討では，全体に賦活が小さく，また語流暢課題遂行中の脳血流量の増加が遅延傾向にあることが示され，前頭葉機能の低下が考えられた（Nishimura et al., 2006)。ここで，パニック障害・第一度親族にパニック障害が1人以上いる群（N=9）と近親者にパニック障害の家族歴および精神科受診や服薬のない群（N=83）との比較，すなわちパニック障害・精神疾患家族歴（PD）の有無による比較を行ったところ，家族歴のあるパニック障害の前頭葉の内側部において有意に［oxy-Hb］の賦活が小さいことが示され，何らかの遺伝的関与が考えられた。

3．Catecol-O-methyl-transferase（COMT）（22q11-13）多型およびmonoamine oxidase A（MAOA）（Xp11.23）の多型における検討

パニック障害におけるCOMT多型による分類：群別プロフィールについては有意な差は認められなかったが，COMT多型別にみた語流暢課題遂行中の前頭葉機能（NIRS）に変化が見られた。特にパニック障害との関与が示されているLL型で異なる賦活が示された。また，パニック障害（男性）においてMAOA多型別にみた語流暢課題遂行中の前頭葉機能（NIRS）で，一部のCH（部位）において，MAOA 3 repeatタイプ（N=7）の［oxy-Hb］の賦活が小さいことが示され，前頭葉機能において何らかの遺伝的因子の関与が示唆された。

ハミルトンらは連鎖研究においてCOMT遺伝子およびその近傍のSNPs（COMT Val158Met多型を含む）における連鎖を報告した（Hamilton et al., 2002)。Rotondoらは双極性障害とパニック障害の合併/非合併例において，catecol-O-methyl-transferase（COMT） Val158Met多型との関連についての検討を行い，パニック障害を合併しない双極性障害において最も強い相関を認めた（Rotondo et al., 2003)。我々が行ったパニック障害とCOMT L/L多型との関連について（Tawara et al., unpublished data)，Wooらの先行研究と同様の結果が得られ（Woo et al., 2002, Woo et al., 2004)，COMTLAlleleがパニック障害の疾患感受性と相関していることが追試された。また，パニック障害が女性に多いという疫学的な統計があり，パニック障害という表現型が男女で不均等に分布する理由を説明する上でCOMTは一つの有力な候補遺伝子である。事実，COMT欠失マウスの行動プロフィールにおいてオスはより「攻撃的」で，メスはより「不安が強い」傾向があるという性差が認められている。そして，ヒトにおいてはCOMT遺伝子型が男性では強迫性障害（OCD）と女性ではパニック障害に関連しているという傾向がある（Gogos et al., 1998；Karayiorgou et al.1999；Hamilton et al., 2002)。115人のパニック障害患者を用いたDomschkeらの研究において，COMT Val158Met多型が女性におけるパニック障害と関連があるとされた（Domschke et al., 2004)。性差がCOMT遺伝子型に関連する表現型で重要な役割を果たす可能性があるため，我々は性別を一致させた健常者コントロールを用いて，性が遺伝子効果に影響するかを検討した。しかし，性別と診断によって対象者を検討したところ，男女ともパニック障害ではL/L遺伝子型が増加する傾向があったが，有意差は認められなかった。女性においてパニック障害と関連する遺伝子部位を見出すことは今後の課題である。また，COMT遺伝子型の分布は民族の人口で異なる。COMTLの対立遺伝子座頻度は，Caucasiansでは約50％と，中国人では18％，日本人では29％である。L/L遺伝子型の頻度は，Caucasiansでは約25％，中国人で3％，日本人では6％であった（Eaton et al., 1994, Li et al., 1997, Ohara et al., 1998)。韓国では，COMTLの割合は23.0％，L/L遺伝子型は4.9％であった。この比率は他のアジアの国においてもほぼ同等である。本研究においてはL/L型は4.3％であった。

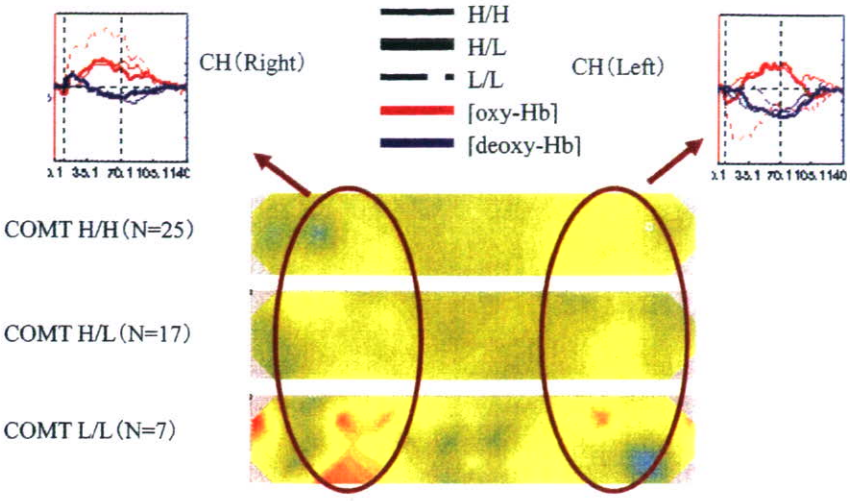

図3　COMT多型別にみた語流暢課題遂行中の前頭葉機能（NIRS）

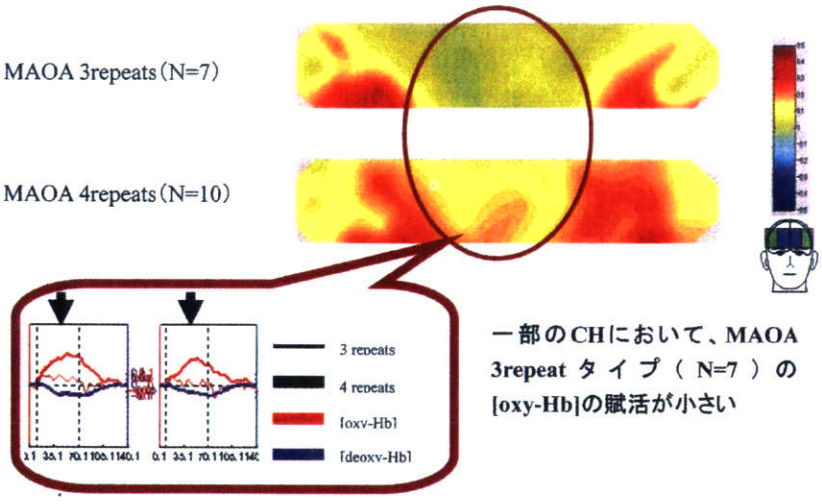

図4　MAO多型別にみた語流暢課題遂行中の前頭葉機能（NIRS）

アジア人においてCOMTL頻度は比較的低くなっており，パニック障害におけるCOMT遺伝子多型の果たす役割を示唆している。台湾，韓国，および日本のパニック障害の生涯有病率は各々，0.4％，1.7％，1−3％と低くなっている。一方，米国における生涯有病率は3.5％と高値を示す（Aoki et al., 1994, Weissman et al., 1997, Hwu et al., 1998, Kaiya et al., 2005）。したがって，アジア人における，COMTL遺伝子型の頻度が低くなっていることはパニック障害の有病率に民族差のあることを説明する可能性がある。

また，精神疾患とMAOAとの関連については，双極性障害における自殺（Ho et al., 2000）や反復性の大うつ病性障害（Schulze et al., 2000）において女性との関連が見出されている。パニック障害が女性に多いという疫学的な統計とMAOA遺伝子X染色体上にあることへの関連性が考えられるため，パニック障害とX染色体との関連については十分な検討がなされるべき課題であると思われる。この関連の報告としては，Deckertらがドイツ人（n=80）とイタリア人（n=129）のサンプルにおいてモノアミンオキシダーゼA遺伝子（Xp）のプロモーター領域の繰り返し配列の伸長した多型が主に女性のパニック障害患者で認められ多く

見られることを報告し（Deckert et al., 1999），伸長した場合にルシフェラーゼ活性を高めることから，モノアミンオキシダーゼAの活性の増加がパニック障害と関連していると考察している。

4．ま と め

以上の結果はパニック障害における前頭葉機能の低下が遺伝的因子によっても制御される可能性を示している。Gormannらによるパニック障害の神経解剖学的仮説ではPET，SPECT研究でパニック障害患者の前頭葉機能低下が示唆され，発作に対する“破滅的な”解釈や回避に関連すると考えられている（Gormann et al., 2000）。パニック障害は遺伝的負因とともに他の身体疾患との関連性や身体的な症状が特徴的であり，発現する症状による分類など新たなアプローチの方法も考慮しつつ研究が進められることが重要である。今後，このような遺伝的研究が更に発展することにより，パニック障害についての的確な診断が可能となることで，脆弱性因子の解明に基づく予防，そしてより個体の状況に合わせた効果的な治療などが期待される。

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