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A positive correlation between serum levels of mature brain-derived neurotrophic factor and negative symptoms in schizophrenia

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ABSTRACT

A meta-analysis study reported serum brain-derived neurotrophic factor (BDNF) levels as a potential biomarker for schizophrenia. However, at the time, commercially available human ELISA kits were unable to distinguish between pro-BDNF (precursor BDNF) and mature BDNF, because of limited antibody specificity. Here, we used new ELISA kits, to examine serum levels of mature BDNF and matrix metalloproteinase-9 (MMP-9), which converts pro-BDNF to mature BDNF in schizophrenia. Sixty-three patients with chronic schizophrenia and 52 age- and sex-matched healthy controls were enrolled. Patients were evaluated using the Brief Psychiatry Rating Scale, the Scale for the Assessment of Negative Symptoms (SANS) and neuropsychological tests. Neither serum mature BDNF nor MMP-9 levels differed between patients and controls. In male subgroups, serum MMP-9 levels of smoking patients were higher than those of non-smoking patients, but this was not observed in male controls or the female subgroup. In patients, serum mature BDNF levels were associated with SANS total scores and the Information subtest scores of the Wechsler Adult Intelligence Scale Revised (WAIS-R), while serum MMP-9 levels were associated with smoking and category fluency scores. These findings suggest that neither mature BDNF nor MMP-9 is a suitable biomarker for schizophrenia, although further studies using large samples are needed.

1. Introduction

Accumulating evidence implicates brain-derived neurotrophic factor (BDNF) in the pathophysiology of schizophrenia (Autry and Monteggia, 2012; Favalli et al., 2012; Martinotti et al., 2012; Nurjono et al., 2012). A meta-analysis suggested reduced blood BDNF levels in patients with schizophrenia, regardless of medication exposure and gender, and an association between reduced BDNF levels in schizophrenia and increasing age (Green et al., 2011). A number of studies have also reported reduced blood BDNF levels in patients with schizophrenia (Chen da et al., 2009; Fernandes et al., 2010; Pillai et al., 2010; Rizos et al., 2010a; Rizos et al., 2010b; Lee et al., 2011; Rizos et al., 2011; Yang et al., 2011; Zhang et al., 2012a; Zhang et al., 2012b; Zhang et al., 2012c). In contrast, several case-control studies have found increased peripheral blood BDNF levels in patients with schizophrenia (Reis et al., 2008; Domenici et al., 2010). We previously reported that serum levels of BDNF in schizophrenics were indistinguishable from those of healthy controls (Shimizu et al., 2003; Niitsu et al., 2011), a finding replicated by other studies (Huang and Lee, 2006; Mackin et al., 2007; Goto et al., 2011). As yet, there is no plausible explanation for this heterogeneity of findings and thus the role of BDNF in schizophrenia pathophysiology remains unclear.

Mature BDNF is synthesized as a precursor protein, pre-pro-BDNF, in the endoplasmic reticulum. Following cleavage of the signal peptide, pro-BDNF is converted to mature BDNF, by extracellular proteases, such as matrix metalloproteinase-9 (MMP-9) and plasmin (Lu, 2003; Hwang et al., 2005; Lu et al., 2005; Ethell and Ethell, 2007; Hashimoto, 2007, 2010, 2013). It was initially thought that only secreted mature BDNF was biologically active, and that pro-BDNF, which localizes intracellularly, served as an inactive precursor. However, new evidence shows that pro-BDNF and mature BDNF elicit opposing effects via the p75NTR and TrkB

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receptors, respectively, and that both pro- and mature BDNF play important roles in several physiological functions (Lu, 2003; Lu et al., 2005; Hashimoto, 2007, 2010, 2013). Considering the physiological importance of both proteins, it would be informative to measure individual levels of pro-BDNF and mature BDNF in human body fluids (Hashimoto, 2010, 2012, 2013). A previous study reported increased serum levels of mature- and pro-BDNF, and decreased serum levels of truncated BDNF in patients with schizophrenia, as measured by western-blotting (Carlino et al., 2011). Although BDNF levels in human blood can be measured using newer commercially available human BDNF, enzyme-linked immunosorbent assay (ELISA) kits, earlier versions of these kits were unable to distinguish between pro-BDNF and mature BDNF due to the limited specificity of the BDNF antibody (Yoshida et al., 2012a; Yoshida et al., 2012b). It is highly possible that the limited specificity of these ELISA kits has contributed to the heterogeneity of results in previous studies examining blood BDNF levels in schizophrenics.

MMP-9 plays a key role in synaptic plasticity of the brain, and acts by converting pro-BDNF to mature BDNF (Hwang et al., 2005; Ethell and Ethell, 2007). A study using MMP-9 knock-out mice demonstrated that MMP-9 plays a role in the development of pentylenetetrazole-induced kindling, by converting pro-BDNF to mature BDNF in the hippocampus (Mizoguchi et al., 2009). Another study suggested that serum levels of MMP-9 increased in patients with major depressive disorder and schizophrenia (Domenici et al., 2010). Therefore, it is plausible that serum levels of both mature BDNF and MMP-9 could play roles in the pathophysiology of schizophrenia.

Considering the evidence presented above, we hypothesized that in patients with schizophrenia, serum levels of mature BDNF and MMP-9 would be higher than those of the healthy controls. In this study, we examined serum levels of mature BDNF and MMP-9 in patients with chronic schizophrenia, and their association with demographic and clinical variables, including cognition.

2. Methods

2.1. Study design

The ethics committee of Chiba University Graduate School of Medicine approved the present study. All subjects provided written informed consent for participation in the study, after the procedure had been fully explained. This study is an exploratory, cross-sectional, and case-control design.

2.2. Participants

Sixty-three Japanese patients with schizophrenia (DSM-IV) were recruited from the outpatient departments of Chiba University Hospital and its affiliated hospitals, in Chiba, Japan. Fifty-two age- and sex-matched healthy Japanese subjects were recruited as healthy controls. Entry criteria of participants are described in detail elsewhere, and this study used the same sample as our previous study (Niitsu et al., 2011).

2.3. Clinical assessments

Clinical symptoms were assessed using the Brief Psychiatry Rating Scale (BPRS) and the Scale for the Assessment of Negative Symptoms (SANS). Drug-induced extrapyramidal symptoms were evaluated using the Drug Induced Extrapyramidal Symptoms Scale (DIEPSS). Intelligence quotient (IQ) scores were estimated using the short version of the Japanese Wechsler Adult Intelligence Scale Revised (WAIS-R), which consisted of the Information, Digit Span, and Picture Completion subtests. Age at onset, duration of illness, duration of untreated psychosis and smoking status were evaluated.

2.4. Cognitive assessments

Cognitive assessments of participants were performed by neuropsychological tests. Details of cognitive assessments and results are available elsewhere (Niitsu et al., 2011). Briefly, participants were assessed using the Verbal Fluency Test (letter, category) (Sumiyoshi et al., 2005), the Wisconsin Card Sorting Test (WCST, Keio version) (the number of achieved categories and perseverative errors) (Igarashi et al., 2002; Hori et al., 2006), the Trail Making Test (Part A and Part B), and the Stroop Test (Part D, a list of 24 colored dots; Part C, 24 words naming a color, written in an incongruent color) (Carter et al., 1995; Chan et al., 2004).

2.5. Measurement of mature BDNF and MMP-9 levels from serum

Serum samples of participants were collected between 10:00 and 13:00 h and stored at −80 °C until assayed. Levels of mature BDNF and MMP-9 were measured using a human BDNF ELISA Kit (Adipo Bioscience, Santa Clara, CA, USA) and a human MMP-9 ELISA Kit (R&D Systems, Minneapolis, MN, USA), respectively. To minimize assay variance, serum levels of mature BDNF and MMP-9 from each subject were measured on the same day. All experiments were performed in duplicate. Protocols were performed according to the manufacturer's instructions. The optical density of each well was measured using an automated microplate reader (Emax; Molecular Devices, Sunnyvale, CA, USA).

2.6. Statistical analysis

For the comparisons between groups, the Chi-squared test was employed for categorical variables, and Student's *t*-test for continuous variables. Two-way analysis of variance (ANOVA) was employed to examine the effects of diagnosis and gender on serum levels of mature BDNF and MMP-9. Effects of smoking status stratified by gender were also examined. Bonferroni correction was used for post hoc tests. Associations between serum levels of mature BDNF and MMP-9, and clinical and cognitive variables were tested for, using Pearson's correlation coefficients and stepwise multiple regression analysis. Since serum levels of MMP-9 did not show normal distribution, the logarithm transformation was used for this variable. Statistical analyses were performed in two-sided tests using SPSS, version 18.0 J software (IBM, Tokyo, Japan). The statistical significance was set at $P<0.05$ with power $(1-\beta)=0.80$. ANOVAs with a total of 115 samples and 52 male samples would have enabled us to detect the following effect sizes: $f=0.31$ (medium-to-large) and 0.48 (large).

3. Results

3.1. Demographic data and clinical variables

Characteristics of the participants are shown in Table 1. Gender, age, education and smoking status did not differ between patients and healthy controls. The proportions of smokers between patients and controls differed in the male (Fisher's exact test, $P=0.04$) but not female subgroup ($P>0.05$) (Tables 2 and 3). The correlations of cognitive data with serum levels of mature BDNF

Table 1
Sample characteristics.

	Controls ($n=52$)	Patients ($n=63$)	*P*
Gender (Male/female)	25/27	26/37	NS[a]
Age (years)	34.9 (7.3)	35.9 (8.2)	NS
Education duration (years)	14.7 (2.7)	13.8 (2.3)	NS
Smoking status (No/yes)	43/9	45/18	NS[a]
Estimated IQ	110.2 (12.0)	102.4 (13.9)	<0.01
Age at onset of illness (years)	–	26.8 (7.0)	–
Duration of illness (years)	–	9.1 (7.3)	–
DUP (months)	–	8.1 (13.4)	–
BPRS	–	25.5 (7.5)	–
SANS	–	70.4 (11.8)	–
DIEPSS	–	2.7 (2.7)	–
Antipsychotic dose (mg/day) [#]	–	323.9 (184.2)	–
Mature BDNF (ng/ml)	28. 10 (7.18)	29.79 (6.09)	NS
MMP-9 (ng/ml)	672.49 (378.36)	700.92 (330.81)	NS

Values represent mean (S.D.). NS, not significant.
Abbreviations: DUP, Duration of Untreated Psychosis; BPRS, Brief Psychiatric Rating Scale; SANS, Scale for the Assessment of Negative Symptoms; and DIEPSS, Drug Induced Extra-Pyramidal Symptoms Scale.
[a] χ^2 test. Other *p*-values are calculated by Student's *t*-test.
[#] Chlorpromazine equivalent dose ($n=60$).

Table 2
Serum levels of mature BDNF (ng/ml).

	Controls (n=52)		Patients (n=63)		Diagnosis		Gender		Diagnosis × gender	
		n		n	F	P	F	P	F	P
Gender					2.09	NS	1.17	NS	0.03	NS
Male	28.70 (7.97)	25	30.70 (6.61)	26						
Female	27.54 (6.46)	27	29.16 (5.71)	37						
							Smoking		**Diagnosis × smoking**	
							F	P	F	P
Total					3.48	NS	0.25	NS	1.66	NS
Nonsmokers	28.57 (7.58)	43	29.45 (4.89)	45						
Smokers	25.85 (4.48)	9	30.66 (8.51)	18						
Male (n=51)					1.80	NS	0.16	NS	1.45	NS
Nonsmokers	29.44 (8.67)	20	29.77 (4.62)	13						
Smokers	25.70 (3.11)	5	31.64 (8.23)	13						
Female (n=64)					0.65	NS	0.46	NS	0.02	NS
Nonsmokers	27.80 (6.58)	23	29.32 (5.06)	32						
Smokers	26.04 (6.37)	4	28.10 (9.67)	5						

Values represent mean (S.D.). NS, not significant. Statistical values are calculated by two-way ANOVA.
Abbreviation: BDNF, Brain-derived neurotrophic factor.

Table 3
Serum levels of MMP-9 (ng/ml).

	Controls (n=52)		Patients (n=63)		Diagnosis		Gender		Diagnosis × gender	
		n		n	F	P	F	P	F	P
Gender					0.37	NS	0.16	NS	0.01	NS
Male	676.5 (451.1)	25	706.3 (369.8)	26						
Female	668.8 (304.9)	27	697.2 (305.7)	37						
							Smoking		**Diagnosis × smoking**	
					F	P	F	P	F	P
Total (n=115)					1.33	NS	2.54	NS	2.14	NS
Nonsmokers	675.5 (400.1)	43	637.2 (305.5)	45						
Smokers	658.2 (267.9)	9	860.3 (346.3)	18						
Male (n=51)					0.23	NS	2.39	NS	4.60	0.037 [a]
Nonsmokers	688.8 (479.3)	20	527.9 (290.3)	13						
Smokers	627.5 (354.7)	5	884.6 (362.9)	13						
Female (n=64)					0.18	NS	0.92	NS	0.001	NS
Nonsmokers	664.0 (327.0)	23	681.5 (304.6)	32						
Smokers	696.4 (142.2)	4	797.3 (328.5)	5						

Values represent mean (S.D.). NS, not significant. Statistical values are calculated by two-way ANOVA with log-transformed serum levels of MMP-9.
Abbreviation: MMP-9, Matrix Metalloproteinase-9.
[a] Post hoc test revealed a significant difference between smokers and non-smokers in male patients with schizophrenia (P=0.004).

and MMP-9 are shown in Table 4. Mean estimated IQ of patients with schizophrenia was significantly lower than that of the healthy controls ($P<0.01$). Furthermore, patients with schizophrenia showed significantly lower scores in all neuropsychological tests ($P<0.05$) (Niitsu et al., 2011).

3.2. Serum mature BDNF levels and MMP-9

Serum levels of mature BDNF did not differ between the diagnosis groups (Table 1). Two-way ANOVA on serum levels of mature BDNF showed no significant effects for diagnosis and gender, or for diagnosis and smoking status (Table 2). After stratification by gender, two-way ANOVA on serum levels of mature BDNF showed no significant effects for diagnosis and smoking status, and their interaction (Table 2). In patients with schizophrenia, serum levels of mature BDNF showed no significant differences among the four types of antipsychotic medications: risperidone (31.20 ± 6.81 [mean ± S.D., ng/mL], n=25); olanzapine (28.34 ± 5.76, n=18); aripiprazole (30.48 ± 5.46, n=9); and quetiapine (27.25 ± 5.43, n=8); (P=0.296).

Serum levels of MMP-9 did not differ between the diagnosis groups (Table 1). Two-way ANOVA on serum levels of MMP-9 showed no significant effects for diagnosis and gender, or diagnosis and smoking status (Table 3). However, in the male subgroup, after stratification by gender, a significant interaction effect for diagnosis and smoking status was observed in MMP-9 serum levels (P=0.037). This effect was not observed in the female subgroup (Table 3). Simple effects analysis revealed that serum levels of MMP-9 in male smoking patients were significantly higher than those in male non-smoking patients (P=0.004). In patients with schizophrenia, serum levels of MMP-9 showed no significant differences among the four types of antipsychotic medication:

Table 4
Cognitive data and their correlation coefficients with serum levels of mature BDNF and MMP-9.

	Cognitive data		Correlation coefficients			
	Controls ($n=52$)	Patients ($n=63$)	Mature BDNF		MMP-9 [a]	
			Controls	Patients	Controls	Patients
Estimated IQ	110.2 (12.0)	102.4 (13.9)	−0.167	0.245	−0.108	-0.131
Information	11.1 (2.6)	10.1 (2.7)	−0.245	0.271*	−0.081	−0.123
Digit span	11.7 (2.9)	10.6 (2.9)	−0.029	0.199	−0.087	−0.138
Picture completion	11.0 (1.9)	10.5 (2.2)	0.033	−0.034	0.054	0.066
Letter fluency test (words)	35.2 (9.0)	28.0 (8.9)	−0.102	−0.021	−0.096	−0.170
Category fluency test (words)	49.1 (6.8)	39.9 (6.9)	−0.163	−0.017	−0.017	−0.323**
WCST, accomplished categories (n) [b]	4.9 (1.5)	3.3 (2.2)	−0.154	0.157	0.071	0.080
WCST, perseverative errors (n) [b]	0.9 (1.8)	4.5 (6.7)	0.149	−0.064	−0.120	−0.079
Trail making test A (s)	27.2 (7.7)	33.8 (10.1)	0.081	0.254*	0.141	−0.090
Trail making test B (s)	52.9 (16.0)	80.5 (27.1)	0.001	−0.034	0.083	0.071
Stroop Test part D (s)	12.7 (2.5)	14.2 (2.6)	0.259	0.146	0.200	0.110
Stroop test part C (s)	18.6 (5.3)	22.7 (5.9)	0.078	0.157	0.157	0.182

Cognitive data represent mean (S.D.).
Abbreviations: BDNF, Brain-derived neurotrophic factor; MMP-9, Matrix Metalloproteinase-9; WCST, Wisconsin Card Sorting Test.
[a] Log-transformed serum levels of MMP-9 are used.
[b] Spearman's correlation coefficients are calculated for WCST. The other statistical values represent Pearson's correlation coefficients.
* $P<0.05$.
** $P<0.01$.

risperidone (747.1 ± 318.8 [mean ± S.D., ng/mL], $n=25$); olanzapine (585.3 ± 284.7, $n=18$); aripiprazole (843.3 ± 454.8, $n=9$); and quetiapine (662.6 ± 332.4, $n=8$); ($P=0.172$).

3.3. Association between mature BDNF levels and clinical variables

Regression analysis revealed no association between serum levels of mature BDNF and MMP-9 in the combined samples, healthy controls, or patients with schizophrenia ($P>0.05$). In schizophrenics, serum levels of mature BDNF were positively associated with SANS total scores ($\beta=0.40$, $P=0.001$) and the Information subtest of WAIS-R ($\beta=0.29$, $P=0.014$), suggesting that higher serum levels of mature BDNF were independently associated with more severe negative symptoms and better performance in the Information subtest. The Trail Making Test Part A was excluded from the stepwise regression model. These associations continued to be significant after adjustment for age, gender and education (SANS total score, $\beta=0.41$, $P=0.001$; Information subtest, $\beta=0.31$, $P=0.014$). In healthy controls, there was no significant association between serum levels of mature BDNF and any other variables. In combined samples, serum levels of mature BDNF were positively associated with Stroop D test scores ($\beta=0.23$, $P=0.015$), implying that higher serum levels of mature BDNF were associated with lower performances in the Stroop D test (naming colors of dots). However, this association was not significant after adjustment for diagnosis, age, and gender.

3.4. Association between MMP-9 levels and clinical variables

In combined samples, serum levels of MMP-9 were positively associated with age ($\beta=0.20$, $P=0.029$) and smoking status ($\beta=0.18$, $P=0.049$), indicating that higher serum levels of MMP-9 were independently associated with older age and smoking. These associations continued to be significant after adjustment for diagnosis and gender (age, $\beta=0.20$, $P=0.031$; smoking status, $\beta=0.20$, $P=0.035$). In healthy controls, serum levels of MMP-9 were positively associated with age ($\beta=0.49$, $P<0.001$). In schizophrenics, serum levels of MMP-9 showed positive association with smoking status ($\beta=0.28$, $P=0.031$) and negative association with the Category fluency test ($\beta=-0.25$, $P=0.047$), suggesting that higher serum levels of MMP-9 were independently associated with smoking and lower performance in the Category fluency test. These associations continued to be significant after adjustment for age, gender and education (smoking status, $\beta=0.35$, $P=0.011$; the Category fluency test, $\beta=-0.29$, $P=0.025$).

4. Discussion

We found no differences in serum levels of mature BDNF or MMP-9 between chronically medicated patients with schizophrenia and healthy controls. In the male but not female subgroup, we detected an interaction effect between diagnosis and smoking status for serum levels of MMP-9. Post hoc analysis revealed that serum levels of MMP-9 in male smoking schizophrenics were significantly higher than those in male non-smoking patients.

The mature BDNF ELISA kits used in this study are able to distinguish between the two forms of BDNF and identify mature BDNF from human serum (Yoshida et al., 2012a; Yoshida et al., 2012b). Although a previous study suggested increased mature BDNF levels in patients with schizophrenia, as measured by western-blotting (Carlino et al., 2011), we found no difference between serum mature BDNF levels in patients and healthy controls. This finding is consistent with several previous studies (Shimizu et al., 2003; Huang and Lee, 2006; Mackin et al., 2007; Goto et al., 2011; Niitsu et al., 2011), although in these studies there was no distinction between BDNF isoforms. In addition, serum levels of mature BDNF and MMP-9 remained the same, independent of the atypical antipsychotic treatment. To determine the effects of antipsychotics on serum levels of mature BDNF in schizophrenic patients, further studies using drug-naïve samples are needed.

The influence of smoking on serum BDNF levels remains controversial. A previous study which did not distinguish between BDNF isoforms, showed that serum BDNF levels were significantly higher in male smoking schizophrenic patients compared with male non-smoking patients (Zhang et al., 2010). However, we found no such effects of smoking on mature BDNF serum levels, in total samples or gender specific subsamples. Therefore, additional studies that distinguish between BDNF isoforms will be needed to determine the effects of smoking on serum BDNF levels.

No association between levels of mature BDNF and MMP-9 was found, although MMP-9 plays an important role in the conversion of pro-BDNF to mature BDNF (Hwang et al., 2005; Ethell and

Ethell, 2007). We found that higher serum levels of mature BDNF in schizophrenics were associated with more severe negative symptomology. This finding is consistent with previous studies examining the same sample set (Niitsu et al., 2011) and a completely different sample set (Reis et al., 2008), although these studies did not distinguish between BDNF isoforms. Additionally, we found that higher levels of mature BDNF in patients were associated with a better performance on the Information subtest of WAIS-R, but not on other cognitive tests. This finding may support a recent study which suggested that serum BDNF levels were positively associated with immediate memory performance in chronic patients with schizophrenia (Zhang et al., 2012b), although again, this study did not distinguish between BDNF isoforms. With regards to other proteolytic BDNF isoforms, a previous study suggested that reduced serum levels of truncated-BDNF (a proteolytic BDNF isoform of 28 kDa), but not mature BDNF, correlated with higher positive and lower negative PANSS scores and a poorer performance in all cognitive assays (Carlino et al., 2011). Recently, Carlino et al. proposed a hypothesis stating that deficits in pro and mature BDNF expression may lead to different types of cognitive deficits (Carlino et al., 2013), and our findings go some way to support this hypothesis. Thus, further studies examining the association between the BDNF isoforms and clinical symptoms and cognitive impairment are still needed.

We found no difference in serum MMP-9 levels between patients with schizophrenia and healthy controls. This finding is inconsistent with the results of a proteomic study, using plasma samples from a large case-control collection, which found increased levels of MMP-9 in both male and female patients with schizophrenia (Domenici et al., 2010). It is worth noting however, that this study included a significantly higher percentage of active smokers in the schizophrenia group, compared with controls. In this study, the proportion of male smoking schizophrenics was higher than that of male smoking controls, although this difference was not present in the female subgroup. Interestingly, we found that, in male patients, serum MMP-9 levels in smokers were higher than those of non-smokers, while this was not the case in male controls. It is likely therefore that MMP-9 serum levels in male patients with schizophrenia are affected by smoking. In females, the discrepancy in MMP-9 levels between our results and a previous study (Domenici et al., 2010) may be attributed to the difference in the proportion of smokers between the two studies. In summary, we found that serum MMP-9 levels were associated with age in healthy controls, and smoking status and performance of the Category fluency test in patients with schizophrenia. While the role of serum MMP-9 in the pathophysiology of schizophrenia is currently unclear, further studies are needed to confirm its association with these factors.

As with similar studies, this study has a number of limitations, the most prominent being the small sample size. It is clear that future studies will need larger cohort numbers. Next, the proportion of smokers in the male subgroup differed between patients and controls. This limitation may produce biases in our observations. Finally, we did not examine the levels of pro-BDNF and truncated-BDNF. It is possible that serum levels of BDNF isoforms play a role in the pathophysiology of schizophrenia (Carlino et al., 2011), and therefore it would be of great interest to study the relationship between serum levels of BDNF isoforms, as well as levels of extracellular peptidases (e.g., MMP-9, plasmin) that convert pro-BDNF to other BDNF isoforms.

In conclusion, we found that serum levels of mature BDNF and MMP-9 showed no difference between patients with schizophrenia and controls. However, in male patients only, serum MMP-9 levels of smokers were higher than those of non-smokers. We also found that in patients with schizophrenia, serum mature BDNF levels were associated with negative symptoms and Information subscale scores of WAIS-R, while serum MMP-9 levels were associated with smoking status and Category fluency performance. Further studies measuring the serum levels of mature BDNF and MMP-9 using larger cohorts are needed to examine the results of this study.

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Competing interests

The authors declare that they have no competing interests.

Author contributions

Conception and design: TN, DM, YS, KH, MI. Serum sampling and assay: TI, TY, TH. Analysis and interpretation of data: TN, KH. Drafting the article: TN. Critical review: TY, DM, YS, MN, ES, KH, MI. Final approval of the article: TN, TI, TY, TH, DM, YS, MN, ES, KH, MI.

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Transporting Cognitive Behavioral Therapy (CBT) and the Improving Access to Psychological Therapies (IAPT) Project to Japan: Preliminary observations and service evaluation in Chiba

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Transporting **Cognitive Behavioral Therapy (CBT) and the Improving Access to Psychological Therapies (IAPT) Project** to Japan: Preliminary observations and service evaluation in Chiba

RUNNING HEAD: Transporting CBT/IAPT to Japan

Abstract

Purpose: This paper discusses the implementation and evaluation of a cognitive behavioral therapy (CBT) training course for clinicians in Chiba, the sixth-largest **province** in Japan.

Design/methodology/approach: Individual CBT for obsessive-compulsive disorder, bulimia nervosa, **or** social anxiety disorder was delivered by trainees of the Chiba CBT training course **in** a single study design.

Findings: The results demonstrated that individual CBT delivered by trainees **led** to **statistically** significant reductions in symptom severity **for all** three disorders. **Feedback from the trainees indicated that the training course achieved its aims.**

Implications: Barriers to the dissemination of CBT in Japan **such as opportunities for training** and possible solutions are discussed.

Originality: This paper evaluates the Chiba CBT training course, which is a Japanese adaptation of the UK Improving Access to Psychological Therapies Project and the first post-qualification CBT training course in Japan.

Keywords: anxiety, cognitive behavior therapy, eating disorders, psychotherapist training, psychotherapist supervision, psychologist development, outcome research

Introduction

Barriers to the dissemination of CBT

Among evidence-based treatments, forms of cognitive behavior therapy (CBT) have been consistently shown to be effective across a wide range of disorders. **While some studies have demonstrated the clinical effectiveness of cognitive behavior therapy for adults in routine clinical practice (e.g., Westbrook & Hill, 1998; Westbrook & Kirk, 2005)**, several authors have noted that evidence of the effectiveness of empirically supported treatments in routine practice is rarely available, and often, the evidence may be delivered suboptimally (e.g. Andrews & Titov, 2009; Gunter & Whittal, 2010; Shafran et al., 2009).

Shafran et al. (2009) identified two barriers to the dissemination of CBT. First, commonly held beliefs, such as 'Research trials have limited applicability to clinical practice' and 'Non-specific therapist effects are more important than specific interventions', hamper the availability of CBT. Second, gaps in the current knowledge about training, measuring competence, **key factors in the etiology or maintenance of the treated disorder**, and the minimum dose required for treatment, limit the **widespread** adoption of the protocols to clinical settings (Shafran et al., 2009). Gunter and Whittal (2010) also identified various barriers to the wide-scale dissemination of CBT for anxiety disorders, including those that are applicable to empirically supported treatments in general (e.g. lack of training opportunities, failure to address practitioner concerns), as well as those that may be specific to CBT for anxiety disorders (e.g. practitioner concerns about using exposure interventions). To overcome these barriers, Gunter and Whittal (2010) advise continuing the accumulation of research-based data, advocating and appealing for the required funding and organisational support, and training practitioners to deliver CBT treatments. Advocates of CBT for anxiety disorders will also need to demonstrate that these treatments are cost effective if wide-scale dissemination is to occur.

In order to address the severe under-provision of treatments and the

dissemination of CBT, the UK government has instigated a highly ambitious program, Improving Access to Psychological Therapies (IAPT), by funding the implementation of NICE guidelines for people suffering from depression and anxiety disorders in England. The IAPT program aims to address the under-provision of these treatments by training 3600 new psychological therapists between 2008–2011, which will provide 900,000 people access to treatment, with half of those engaging in treatment moving to recovery, and 25,000 fewer sick pay and medical benefit expenditures by 2010/11. Initial evaluation of two UK demonstration sites, Doncaster and Newham (Clark et al., 2009) has been published, and a two-year prospective cohort study was carried out to assess the impact of implementing empirically supported stepwise psychotherapy programs in routine practice in northern England (Richards & Borglin, 2011).

Status of mental healthcare and CBT in Japan

Awareness of the effectiveness of CBT has spread **in Japan**, not only among professionals and academics but also to the public through media (e.g., books, newspapers, TV). In April 2010, the inclusion of CBT for mood disorders in the national health insurance scheme marked a milestone **for** psychiatric care in Japan, where pharmacotherapy has historically been much more common. The inclusion of CBT in Japan's insurance program is boosting CBT research **through** randomized controlled trials and facilitating training and practice in this field. However, many obstacles **must still be overcome**. For example, CBT for mood disorders is covered by national health insurance only if **it is** provided by medical doctors. Thus, patients bear all costs when other mental health professionals (e.g., clinical psychologists) conduct CBT. In addition, **CBT for other** mental health problems—such as anxiety disorders—are not yet covered by national health insurance. **Most** importantly, there are few competent CBT therapists in Japan, mainly because the opportunities for training are extremely limited **compared to the UK supervision structure in the IAPT services**. There

are workshops during annual conferences, and several institutions, such as the Tokyo CBT Academy and the National Centre for Cognitive Behavior Therapy and Research, regularly provide a series of workshops. **However, only a limited number of clinicians can attend such training because it is primarily in Tokyo. Moreover, the total training time is relatively short (2–50 hours), and supervision is not provided (even when available, it is not provided on a regular basis).**

Chiba University training course

Chiba University was founded in 1949 by uniting several regional national colleges and schools, **including** the Chiba Medical College. The university is located in Chiba **province**, which has a population of approximately **six** million—the sixth largest among the 47 **provinces** in Japan. In 2010, the Graduate School of Medicine at Chiba University set up a CBT training course, the first post-qualification course for CBT in Japan. Trainees who enroll in the course are required to attend a series of workshops **held** over **two** years. **The training day typically consists of a 3-hour workshop in the morning, and a 90-minute clinical case conference, and 60-minute group supervision in the afternoon. In addition, trainees receive 30-minute individual supervision.** The **full course of** training **includes more than** 400 hours. This training course started in April 2010 with **three** supervisors (**two** psychiatrists and **one** psychologist) and 18 trainees; **however, the** numbers of supervisors and trainees are increasing. Most trainees work in Chiba **province** and are psychiatrists, psychologists, psychiatric social workers, nurses, and pharmacologists.

Our training course was inspired and influenced by the IAPT Project in the UK; our project aims to disseminate CBT in Chiba **province** and to increase the number of CBT therapists equivalent to **the** "high-intensity practitioners" in the UK. Similar to the accreditation for high-intensity practitioners, our trainees are required to complete 200 hours of clinical practice, receive 70 hours of supervision, and complete written reports for a

minimum of eight cases. **Along with the written reports, trainees are required to submit audio or a video record of the sessions, and their competence in each session is assessed by supervisors using the Revised Cognitive Therapy Scale (CTS-R: Blackburn et al., 2000).** The major differences between **the** UK IAPT and our course are **the frequency that** trainees come to the university for the course and how this training is funded. Because the trainees do not receive government funding, they attend the course only once per week for **two** years, and their training is funded by their employers. For those with limited opportunity to conduct individual psychotherapy at their own workplaces, the course also provides placement at Chiba University Hospital, where trainees see patients with anxiety disorders or bulimia nervosa (BN). **Furthermore, our course, unlike the UK IAPT, offers follow-up supervision sessions, in which trainees received 30-minute individual supervision once a month for one year after the completion of the course. Moreover, some trainees go on to a PhD course and continue to attend the program.**

Purpose of the present study

The purpose of this study is to report the preliminary outcomes of individual CBT for obsessive–compulsive disorder (OCD), BN, and social anxiety disorder (SAD) delivered by **the** trainees at Chiba University Hospital. To reflect routine clinical practice, we included patients with comorbid mood disorders if OCD, SAD, **or** BN was the principal diagnosis. The outcomes of trainee-delivered CBT **are** used to measure the effectiveness of our training course. We predicted that CBT would be associated with decreased symptom severity. **Additionally, a post-hoc survey was conducted to receive feedback from the trainees who completed the course.**

Methods

Design

Between April 2010 and December 2011, patients were recruited by clinical referrals from both Chiba University Hospital and other local psychiatric hospitals and clinics; **these patients were assessed by the supervisors at Chiba University Hospital** using the Structured Clinical Interview for Axis I Disorders (SCID-I; First & Gibbon, 1997). Written informed consent was obtained from all participants. The criteria for inclusion in this study included a primary diagnosis of OCD, BN, **or** SAD according to the DSM-IV and 18–65 years **of age.** The exclusion criteria were psychosis, mental retardation, current high risk of suicide, substance abuse or dependence in the past **six** months, antisocial personality disorder, unstable medical condition, pregnancy, or lactation.

After enrolling in the study, the patients were placed on a waiting list. The waiting period was not controlled because it was based on the availability of therapy rooms; the wait averaged 140.90 days (SD = 62.18) for OCD, 89.6 days (SD = 84.5) for BN, and 13.26 days (SD = 3.21) for SAD. After the waiting period, the participants received a **50-minute individual** CBT intervention for 12 weeks. Extra sessions were flexibly added, and termination of treatment was determined jointly by the participants and therapists in consultation with the supervisor. The average number of sessions per participant was 16.25 (SD = 3.77) for OCD, 13.75 (SD = 2.87) for BN, and 13.89 (SD = 1.24) for SAD. **Concominant** medications were permitted if the dose remained stable throughout the study. Participants were assessed using the outcome measures at pre- (first session) and post-CBT (final session).

This study was conducted at an outpatient clinic at Chiba University Hospital, which is used by trainees who have limited opportunities to conduct individual psychotherapy at their own workplaces.

Outcome measures

The primary outcome measures were self-reported obsessive–compulsive symptoms, as measured by the Obsessive Compulsive Inventory distress scale (OCI; Foa et al., 1998); self-reported bulimic symptoms, as measured by the Severity Scale of the Bulimic **Investigatory** Test, Edinburgh (BITE-SS; Henderson et al., 1987); and self-reported symptoms of social anxiety, as measured by the Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987).

General severity of mood and anxiety were measured by the standard measures used in the UK IAPT: the 9-item version of the Patient Health Questionnaire (PHQ-9; Kessler et al., 2002), which has scores ranging from 0 to 27 and a recommended cut-off of ≥10 for distinguishing between clinical and non-clinical populations; and the 7-item version of the Generalized Anxiety Disorder scale (GAD-7; Löwe et al., 2008), which was originally developed to screen for GAD, but also has satisfactory sensitivity and specificity for the detection of other anxiety disorders. These scales are outcome measures commonly used in the UK.

Therapists

CBT was delivered by the trainees in the CBT training program. As a course requirement, they attended 30-minute individual supervision sessions **once every two weeks** and 60-minute weekly group supervision sessions, allowing both supervisors and other trainees to give support and assistance in planning future sessions.

Twenty-two therapists participated in the present study (16 women and six men) with a mean age of 42.13 years (SD = 10.99). In this study, the trainees treated an average of 1.86 patients; most therapiss were allocated 1 or 2 patients. In terms of clinical licenses, there were 13 clinical psychologists, three psychiatrists, one general physician, two psychosocial workers, and three nurses. The average number of years in practice as a clinician was 7.00 years (SD = 6.95), and the average number of days of CBT workshop they had attended before enrolling in our course was 7.47 days (SD = 9.61). The clinical or therapeutic orientation they had used

most in their practice included psychodynamic (n = 1), CBT (n = 3), psychiatric (n = 3), counseling/client-centered (n = 6), integrated/eclectic (n = 7), or a combination of these orientations/other (n = 7).

Interventions

The main steps in the CBT treatment for OCD were:

- Provision of psycho-education about the cognitive-behavioral model of OCD
- Goal setting
- Tailored case formulation
- Exposure and response prevention
- Homework
- Relapse prevention

Therapists were also permitted to use other intervention strategies as needed (e.g., Hougton et al., 2010), including behavioral experiments to test the validity of erroneous beliefs, opinion surveys, and ratings of mastery and pleasure.

Our CBT program for BN was based on Maudsley's model, "Getting Better Bite by Bite" (Schmidt & Treasure, 1993). Getting Better Bite by Bite is the only self-help program that has been evaluated in a randomized controlled trial and provides detailed, step-by-step advice for dealing with BN. The main steps in treatment were:

- Guidelines for behavior change
- Discussion of the pros and cons of maladaptive eating behaviors
- Core values and goal setting
- Psycho-education regarding nutrition, food, and weight
- Self-monitoring using a food diary and provision of a structure for eating
- Action plans on how to stop bingeing and purging behaviors
- Identification of automatic thoughts and modification of maladaptive assumptions and

core beliefs

- Behavioral experiments to challenge maladaptive beliefs
- Progressive actions
- Discussion of remaining challenges
- Dealing with interpersonal difficulties
- Relapse prevention.
- Homework assigned after every session

Our CBT program for SAD was based on the model of Clark and Wells (1995). The main steps in treatment were:

- Developing an individualized version of the cognitive behavioral model of SAD
- Conducting role-play–based behavioral experiments with and without safety behaviors
- Restructuring distorted self-imagery using videotape feedback
- Practicing external focus and shifting attention
- Conducting behavioral experiments to test negative beliefs
- Modifying problematic pre- and post-event processing
- Discussing the difference between self-beliefs and other people's beliefs (reflected in survey results)
- Dealing with remaining assumptions (schema work)
- Rescripting early memories linked to negative images in social situations
- Preventing relapse
- Homework assigned after every session

Statistical analysis

The outcomes of the CBT treatment were **examined by the comparison of** pre- and post-CBT scores **of** each scale (OCI, BITE-SS, LSAS, PHQ-9, and GAD-7) using within-group *t*-

tests. Effect sizes **were** determined ($[M_{pre\text{-}CBT} - M_{post\text{-}CBT}]/SD_{re\text{-}baseline}$). According to Cohen (1988), the effect sizes **were** categorized as follows: small (0.20–0.49), medium (0.50–0.79), and large (0.80 and above).

Feedback from trainees

A post-hoc survey via email was conducted with the trainees who took part in this study to obtain their feedback on the training course. They were asked to rate the following questions on a seven-point scale (ranging from very satisfied [7], satisfied [6], slightly satisfied [5], neutral [4], slightly dissatisfied [3], dissatisfied [2] to very dissatisfied [1]):

1. **How satisfied were you with the length (i.e., one day a week for two years) of the training course?**
2. **How satisfied were you with the content and the delivery of the workshops?**
3. **How satisfied were you with the frequency and the duration of the supervision?**

Additionally, they were asked to note the distinctive aspects of our training course compared to the CBT training they had previously and note any difficulties faced during the training.

Results

Results of patients with OCD

Of the 21 patients screened, three were excluded because OCD was not their primary diagnosis (one OCPD, one adjustment disorder, and one hypochondriasis). Eighteen participants satisfied the study criteria and were referred to the study. During the waiting period, four patients declined the treatment without disclosing their reasons. Once the treatment started, the remaining 14 patients completed the study.

Table 1 shows the baseline demographic and clinical variables of the 14 participants (Table 1). Eleven were women (79%), and the participants' mean age was 36.79 years. Five participants (36%) were unemployed, and six (43%) were single. All participants met the principal DSM-IV diagnostic criteria for OCD (mean duration: 5.21 years). Six participants (57%) also met the criteria for major depressive disorder as an additional Axis I diagnosis. Other clinical variables and participants' demographics are shown in Table 1.

Table 1 about here

The primary outcome measure was the severity score of the OCI. The mean OCI score decreased from 64.43 (SD = 3.39) to 32.54 (SD = 17.49) over the course of treatment. The PHQ-9 and GAD-7 scores reduced from 8.57 (SD = 4.09) to 5.07 (SD = 4.29) and from 8.14 (SD = 5.63) to 4.07 (SD = 2.84), respectively. A within-group *t*-test revealed significantly different scores between the pre- and post-CBT scores on the assessed scales: $t(1, 13) = 5.153$, $p < .001$ for the OCI; $t(1, 13) = 2.775$, $p = .015$ for the PHQ-9; and $t(1, 13) = 3.277$, $p = .006$ for the GAD-7. The effect sizes between the pre- and post-CBT were 1.05 (large), .86 (large), and .72 (medium) for the OCI, PHQ-9, and GAD-7, respectively.

Results for patients with BN

Of the 11 subjects screened, one was excluded from the study because her primary diagnosis was not BN (anorexia nervosa binge-eating/purging type). After enrolling in the study, no patients dropped out, but assessment data were not obtained from two patients. As a result, the data of eight patients were subject to analysis.

Table 2 shows the baseline demographic information and clinical variables of the eight patients whose data were analyzed. All of the participants were female, and their mean age was 31.3 years. One patient was employed, three were students, and four were single. Four patients had comorbid psychiatric disorders: two had additional Axis I diagnoses of major depressive disorder, one had bipolar disorder, and one had SAD. Other clinical variables and

participants' demographics are shown in Table 2.

Table 2 about here

The primary outcome measure was the severity score on the BITE-SS. The average BITE-SS score decreased from 9.75 (SD = 4.28) to 4.00 (SD = 4.34) over the course of the study. The PHQ-9 and GAD-7 scores reduced from 12.12 (SD = 7.70) to 8.13 (SD = 7.42) and from 9.38 (SD = 6.12) to 6.25 (SD = 6.67), respectively. A within-group *t*-test revealed significant differences between pre- and post-CBT in BITE-SS, $t(1, 7) = 2.803$, $p = .026$, and GAD-7 scores, $t(1, 7) = 2.739$, $p = .028$. However, there was no significant difference in the PHQ-9 scores over the course of the study, $t(1, 7) = 1.782$, $p = .117$. The effect sizes between pre- and post-CBT were 1.348 (large), .516 (medium), and .508 (medium) for the BITE-SS, PHQ-9, and GAD-7, respectively.

Results for patients with SAD

Of the 23 subjects screened, four were excluded: two had high risk of suicide, and the primary diagnoses of the other two were not SAD (autism spectrum disorders). As a result, 19 patients met the enrolment criteria and were referred to the study. All patients completed the study.

Table 3 shows the baseline clinical variables and demographics of the 19 patients who enrolled in this study (Table 3). Fourteen of the participants were women (74%), and the patients' mean age was 32.3 years. Four patients (21%) were unemployed and 12 (63%) were single. All participants met the principal DSM-IV diagnostic criteria for SAD (mean duration: 14.3 years). Patients with additional Axis I diagnoses included five (26%) who met the criteria for major depressive disorder, two (13%) for bipolar disorder type II, and one (5%) for panic disorder with agoraphobia.

Table 3 about here

The primary outcome measure was the severity score of the LSAS. The average LSAS