Based on the preclinical and clinical evidence that elevation of AVP occurs as a consequence of chronic stress (De Goeij et al., 1992; Watson et al., 2006a), we measured the post-DEX AVP level to investigate whether the blunted cortisol response would reflect allostatic shift toward elevation of AVP or preexisting vulnerability, as stated earlier. Actually, no significant association was seen between the post-DEX AVP level and psychological measures, suggesting that the relation of blunted cortisol response with several psychological measures would not be attributable to the allostatic shift. Rather, the blunted cortisol response observed here could be considered to relate to preexisting non-clinical psychopathology, including the psychological distress and avoidant coping style. This corresponds well to the evidence that low cortisol levels may be a risk factor for psychopathological conditions, in particular PTSD (Yehuda et al., 2000). Simeon et al. (2007) also demonstrated the positive association between resilience and higher urinary cortisol levels in healthy adults. However, caution should be exercised in accepting this argument because evidence from clinical studies that the peripheral AVP level is elevated after chronic stress has not been sufficient to date.

Findings reported here should be interpreted in the context of a number of limitations. First, since the DEX/CRH test used here was based on a simple test protocol (i.e., measuring hormones only twice and omitting the ACTH measures), it may have provided less information on HPA axis hormones than the standard DEX/CRH test measuring both cortisol and ACTH levels at 5 time points between 1500 h and 1615 h. Moreover, we did not measure baseline levels of cotisol or AVP, i.e., those before the DEX challenge, which precluded us from knowing the extent to which each participant suppressed his/her cortisol and AVP secretions in response to the 1.5 mg of DEX. Second, the criteria for the suppression pattern employed here do not have sufficient empirical basis of the literature; however, the consistency between the *a priori* defined grouping (where cut-off values of cortisol were 1 μg/dL and 5 μg/dL) and the other grouping (where cut-off values of cortisol were 1 μg/dL and 13 μg/dL) in terms of their associations with the psychological measures might justify the grouping criteria. Third, this cross-sectional study cannot provide information as to whether the psychological outcomes assessed with the questionnaires were temporary or prolonged ones, nor can it address the natural history of the alteration in HPA axis function. Fourth, we cannot determine from the peripheral AVP measures alone whether they originated from the parvocellular or magnocellular system of PVN. Fifth, we did not collect data on menstrual cycle in the female participants, which may have affected HPA axis function. Sixth, one might think that there would be some biases in our sampling because none of the 93 female subjects reported that they were on oral contraceptives or hormone replacement therapies at the time of the neuroendocrine test. However, this issue should be considered in the context of considerable ethnic differences in the prevalence of these medications; some data show that approximately 1% and 4% of Japanese women were on low-dose oral contraceptives and hormone replacement therapies, respectively (Katanoda et al., 2003; Matsumoto et al., 2003), while that approximately 35–60% and 20–30% of women in Western countries were on low-dose oral contraceptives and hormone replacement therapies, respectively (Mishra et al., 2006; Tanis et al., 2003; Terry et al., 2002). Therefore, the absence of the use of such medications in the present sample could be attributed to the very low prevalence of these medications in Japan, unlike in most Western countries. Finally, as we did not collect data on the history of childhood trauma or maltreatment, which has been repeatedly reported to lead to HPA axis dysfunction in adulthood (Carpenter et al., 2007, 2009; Heim et al., 2008), some findings of the present study (e.g., the association of avoidant coping strategy with enhanced suppression of cortisol) might be confounded by such a history of early-life adversity. However, even if this is the case, our purpose of investigating the cross-sectional relations between HPA axis function and its psychological correlates in non-clinical adults will not be hampered.

In conclusion, the present study found that enhanced suppression, or blunted response, of cortisol in the DEX/CRH test was associated with greater psychological distress and avoidant coping style in a healthy population. This finding further suggests that impaired ability to mount an adequate cortisol response to pharmacological challenge may serve as a biomarker to define certain psychopathology in a non-clinical population. Such a biomarker might be useful to better understand the etiology of mental disorders and risk for symptom development.

Conflict of interest

All authors declare no conflict of interest.

Contributors

HH and HK conceptualized and designed the study, including the literature searches and analyses. HH, YO, TT, JM, YumK, YukK, SS and HK collected the data. HH performed the neuroendocrine testing, undertook the statistical analyses, and wrote the first draft of the manuscript, under the supervision of HK. ST and TH gave critical comment on the manuscript. All authors contributed to and have approved the final manuscript.

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Neuroimaging study in subjects at high risk of psychosis revealed by the Rorschach test and first-episode schizophrenia

Ota M, Obu S, Sato N, Asada T. Neuroimaging study in subjects at high risk of psychosis revealed by the Rorschach test and first-episode schizophrenia.

Objective: There is increasing evidence of neuroanatomical pathology in schizophrenia, but it is unclear whether changes exist prior to disease onset. This study aimed to examine whether changes exist prior to disease onset, especially in the temporal lobes.
Methods: T1-weighted and diffusion tensor magnetic resonance imaging were performed on 9 first-episode schizophrenia patients, 10 patients who were at high risk of schizophrenia and 10 healthy controls. Voxel-based analysis using the normalised images of cortical volume data was examined, and the fractional anisotropy value at three component fibres of the temporal lobes, inferior longitudinal fasciculus, superior longitudinal fasciculus (SLF) and cingulum hippocampal part was compared among the three groups.
Results: There were statistically significant volume differences at the bilateral temporal lobe between the healthy subjects and high-risk group. Between the schizophrenic group and healthy subjects, statistically significant volume differences were detected at the bilateral temporal lobes and anterior cingulated cortex. The fractional anisotropy values of the SLF in the schizophrenic and high-risk groups were significantly lower than in the healthy subjects.
Conclusion: Our findings indicate that some brain alterations may progress in patients at psychosis pre-onset, possibly because of disrupted developmental mechanisms, and these pathological changes may be predictive of functional outcome.

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Keywords: diffusion tensor imaging; magnetic resonance imaging; Rorschach test; schizophrenia; voxel-based morphometry

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Introduction

Structural brain abnormalities have consistently been shown to be present in people with schizophrenia (1–3), and how the brain abnormalities observed in schizophrenia develop is of great interest. Some behavioural features can be observed in patients with schizophrenia years before the onset of illness (4,5), suggesting that there are neural differences from a very early age that may make these individuals more vulnerable to later insults. Early detection and prevention strategies for schizophrenia have led to investigations of individuals at the high risk of psychosis, who present with a constellation of clinical symptoms thought to be characteristic of the psychosis in the 'prodromal period', when the onset of schizophrenia would be expected to occur. Such studies seek to characterise the developmental processes that lead to disturbances of the brain structure and function associated with the onset of psychosis, and to find baseline traits that are predictive of later diagnostic conversion or functional decline. Previous studies mainly used the PACE criteria for the identification of those high risk of development psychosis (6). However, the previous neuroimaging studies adopting showed inconsistent results (7–11).

The Rorschach test has been used historically as a way to identify psychological processes associated

with thought and perceptual disturbance, and to aid in the differential diagnosis of schizophrenia. For the differential diagnosis, the Perceptual Thinking Index (PTI) comprised of eight Rorschach variables that are arranged based on a combination of different values on five empirical criteria was developed (12,13). It measures both perceptual oddities and cognitive slippage, and sufficient (Intraclass Correlation Coefficient >0.8) reliability and validity was also investigated (14). This supports the notion of applying it to the detection of psychosis risk in a clinical population. The preceding studies showed that individuals at clinical high risk for psychosis established using the Structured Interview for Prodromal Symptoms and the Scale of Prodromal Symptoms (SIPS/SOPS; 15) displayed substantial deficits in visual form perception prior to the onset of psychosis revealed by Rorschach test (16,17). Ilonen et al. showed that the PTI distinguished patients at clinical high risk for psychosis from those diagnosed as having non-psychotic disorders (12). The deficits in visual form perception revealed by the PTI fell under the group 1; the attenuated psychotic symptoms of the PACE criteria. In this study, we used the PTI to evaluate patients without delusion, hallucination and catatonic behaviour, but at high-risk mental state for schizophrenia.

Previous cross-sectional imaging studies in schizophrenia found reduced grey matter volume compared to controls, particularly in the temporal lobes, and some studies showed that there were significant differences in temporal lobes between the healthy subjects and pre-onset or at high genetic risk of schizophrenia groups (11,18,19). However, no study investigated the impairment of the component fibres at temporal regions coupled with volume data. In this study, therefore, we first evaluated the cortical volume difference among the pre-onset group, first-episode schizophrenic group and healthy controls. We then investigated the microstructural change among the three groups at three component fibres of the temporal lobes, the inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF) and cingulum hippocampal part that runs along the ventral aspect of the hippocampus.

Method

Subjects

Five male and four female first-episode schizophrenia patients, defined according to the criteria described in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV), were recruited at Hospital Bando (Ibaraki, Japan). Their mean age was 29.0 ± 4.3 years (ranging from 23 to 34 years). Only one patient was drug naive, while the other eight were being treated with antipsychotic medication. The mean interval between the first patient contact and magnetic resonance imaging (MRI) scan was 33.9 ± 21.7 days (ranging from 0 to 70 days).

We also recruited patients who were regarded as having a clinical high risk for schizophrenia but who did not fulfill the schizophrenia criteria. Patients showing the presence of at least one of the following symptoms were tested with the Rorschach test: ideas of reference, magical thinking, perceptual disturbance, paranoid ideation, odd thinking and speech. The individual PTI was scored, and a score of ≥ 1 was regarded as showing perceptual disturbance (16). As a consequence, four male and six female patients (mean age 25.5 ± 11.1 years, ranging from 16 to 46 years, mean PTI score 3.6 ± 0.8) were regarded as at high risk for the developing psychosis.

Exclusion criteria included a history of head injury, neurological symptoms, speech or hearing difficulties, significant cerebrovascular diseases (cortical infarctions, multiple lacunar lesions or leukoaraiosis) and fulfilment of the DSM-IV criteria for abuse of illicit drugs or alcohol at any point during their lifetime.

Ten sex- and age-matched healthy subjects (four males and six females, mean age 26.1 ± 3.8 years, ranging from 16 to 30 years) were also included in the study.

All participants provided their written informed consent, and the local ethics committee approved the study protocol.

Data acquisition and processing

MRI was performed on a 1.5 Tesla Siemens Magnetom Harmony (Erlangen Germany). DTI was carried out on the axial plane (echo time (TE)/repetition time (TR) = 100/7000 ms; field of view (FOV), 262 × 262 mm; matrix 128 × 128; 40 continuous transverse slices; slice thickness, 4 mm with no slice gap). To enhance the signal-to-noise ratio, acquisition was repeated four times. Diffusion was measured along 12 non-collinear directions with the use of a diffusion-weighted factor b in each direction of 1000 s/mm^2, and one image was acquired without the use of a diffusion gradient. High-spatial-resolution, 3-dimensional (3D) T1-weighted images of the brain were obtained for morphometric study. 3D T1-weighted images were scanned on the sagittal plane [TE/TR, 3.93/1460 ms; flip angle, 15°; effective section thickness, 1.5 mm; slab thickness, 168 mm; matrix, 256 × 256; FOV, 250 × 250; 1 number of excitations (NEX)], yielding 112 contiguous slices through the head. In addition to DTI and 3D T1-weighted images, we also acquired

axial T2-weighted turbo spin echo images (TE/TR, 95/3800 ms; slice thickness, 6 mm; intersection gap, 1.2 mm; matrix, 384 × 288; FOV, 220 × 175 mm; acquisition, 1) and fluid attenuation inversion recovery (FLAIR) images on the axial plane (TE/TR, 104/9000 ms; flip angle, 170°; slice thickness, 6 mm; intersection gap, 1.2 mm; matrix, 256 × 192; FOV, 220 × 175 mm; acquisition, 1) to rule out cerebral vascular disease.

The raw diffusion tensor and 3D T1-weighted volume data were transferred to the workstation and the DTI data sets were analysed using DtiStudio (H. Jiang and S. Mori; Johns Hopkins University). The diffusion tensor parameters were calculated on a pixel-by-pixel basis, and the FA map, $b = 0$ image and finally 3D fibre tracts were calculated (20).

To clarify volume differences among the two patient groups and healthy subjects, structural 3D T1-weighted MR images were analysed using an optimised voxel-based morphometry (VBM) technique. Data were analysed using Statistical Parametric Mapping 5 (SPM5) software (Welcome Department of Imaging Neuroscience, London, UK) running on MATLAB 7.0 (Math Works, Natick, MA, USA). Images were processed using optimised VBM script. Details of this process are described elsewhere (21). Normalised segmented images were modulated by multiplication with Jacobian determinants of spatial normalisation function to encode the deformation field for each subject as tissue density changes in normal space. Images were smoothed using an 8-mm full-width half-maximum of an isotropic Gaussian kernel.

To exclude some of the subjectivity involved in defining regions of interest (ROIs), we made fibre ROIs normalised to the standard space, and then placed the ROIs on all of the individual FA images normalised to the standard space for the evaluation of FA. First, each individual 3D-T1 image was coregistered and resliced to its own $b = 0$ image. Next, the coregistered 3D-T1 image was normalised to the 'avg152T1' image regarded as the anatomically standard image in SPM5. Finally, the transformation matrix was applied to the FA map. Each map was then spatially smoothed by a 6-mm full-width half-maximum Gaussian kernel in order to decrease spatial noise and compensate for the inexact nature of normalisation following the 'rule of thumb' developed for functional MRI and positron emission tomography studies (22).

Fibre tractography was performed on the data of 10 healthy subjects with a threshold value of fibre-tracking termination of FA = 0.2 and a trajectory angle of 50° (23). The definition of the bilateral ILF, SLF and cingulum hippocampal part was described in detail in a previous publication (24), and we used these bilateral fibres within the temporal lobe as ROIs. Then, each six fibre tracts of 10 subjects were normalised to the standard space as mentioned above. The normalised six fibre tracts of 10 subjects were averaged respectively, and regarded as the normalised fibre ROIs. Figure 1 shows the fibre ROIs for SLF, ILF and the cingulum hippocampal part on the anatomically standard space.

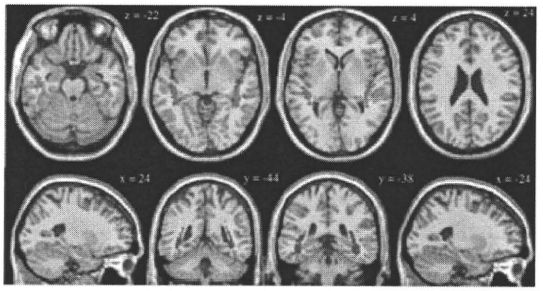

Fig. 1. Diffusion tensor tractography of three fibres. Red, yellow and green fibres represent the inferior longitudinal fasciculus, superior longitudinal fasciculus and cingulum hippocampus part, respectively.

Statistical analysis

Statistical analyses for the grey matter volume were performed using SPM2 software. First, we evaluate the difference among the three groups using the one-way analysis of variance (ANOVA). Only correlations that met these criteria were deemed statistically significant. In this case, seed levels of $p < 0.001$ (uncorrected) were selected. Then, the *post hoc* analysis, the differences in regional grey matter volume between first-episode schizophrenic patients and healthy subjects, high-risk groups and healthy subjects and first-episode schizophrenia and the high-risk groups were assessed using the mask image derived from the result of first-level ANOVA, respectively. Only correlations that met these criteria [seed levels of $p < 0.001$ (uncorrected), and cluster levels of $p < 0.05$ (uncorrected)] were deemed statistically significant.

Statistical analysis for the FA value was performed with SPSS for Windows 11.0 (SPSS Japan, Tokyo, Japan). Group differences of regional FA values among the three groups were compared with repeated measures of ANOVA. When significant group or group × region interactions were obtained with ANOVA, follow-up t-tests were performed for regional FA values of individual ROIs. The least significant difference method was used to avoid type 1 errors in the statistical analysis of multiplicity.

Results

There were significant volume differences in cortical volume among the two patient groups and healthy subjects. First, there were statistically volume differences in the bilateral temporal cortices between the high-risk patients and healthy subjects (Figure 2, upper column; Table 1). Second, volume losses in the bilateral temporal cortices and anterior cingulate cortex (ACC) were detected between the first-episode schizophrenia group and healthy subjects (Figure 2, lower column; Table 1). The locations of the bilateral temporal cortices detected by these analyses were almost the same coordinate (Figure 2). No differences were detected between the high-risk patients and first-episode schizophrenia patients in our study (data not shown).

The ANOVA of FA values for the healthy subjects and patient groups showed a significant main effect of group and regions. Follow-up unpaired *t*-tests revealed that the mean FA value of the healthy subjects was significantly higher in the bilateral SLF regions (Table 2) than in the two patient groups.

Table 1. Regions of statistically significant cerebral grey matter volume change among the three groups: one-way ANOVA among the schizophrenia, high-risk patient and healthy subject

Cluster size	*T* score	x	y	z	Brain region
Post hoc analysis					
Healthy subject > high-risk patient					
1024	5.20	−57	−53	−6	Left middle temporal region
730	5.45	66	−33	−9	Right middle temporal region
Healthy subject > first-episode schizophrenia					
1372	5.77	−60	−53	−7	Left middle temporal region
465	5.48	−57	−38	6	Left middle temporal region
807	5.55	66	−35	−8	Right middle temporal region
600	4.69	8	48	−7	Right anterior cingulate
	4.68	−5	48	3	Left anterior cingulate

Discussion

To the best of our knowledge, this is the first investigation of brain alterations in a clinical high-risk sample showing perceptual disturbance revealed by Rorschach test. Perceptual and thought disorders are commonly associated with psychiatric disorders and are particularly considered a primary feature of schizophrenia. Some preceding studies showed that the high-risk populations present disorders of thought, perceptual abnormalities and disorganised speech (16,17,25,26). In this study, we pointed on the perceptual disturbance as the major symptom of the high-risk patients. Furthermore, we found that there were precedent changes in the brains of high-risk patients revealed by 3D-volume data and DTI. This

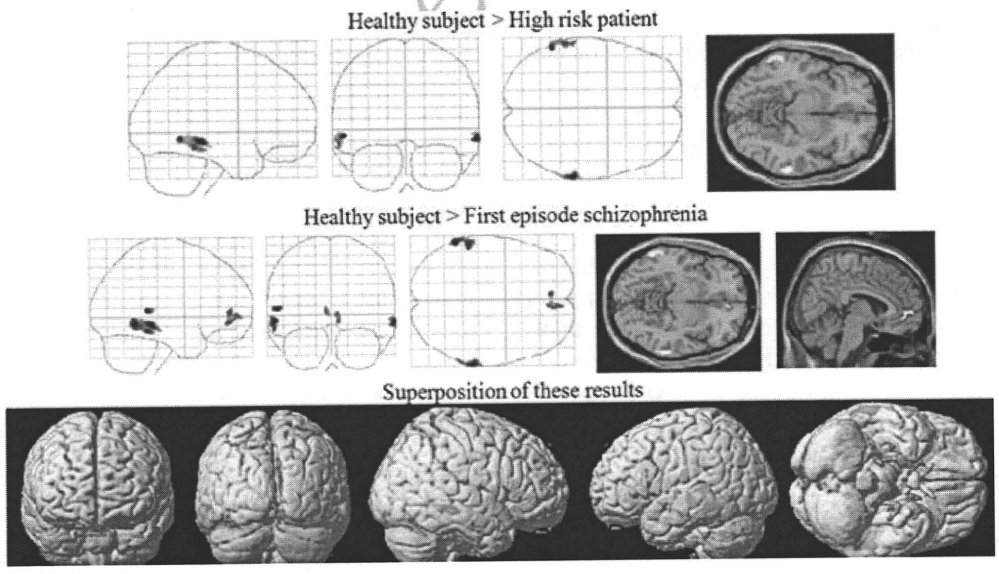

Fig. 2. Cortical grey matter volume loss was detected among the high-risk patients, first-episode schizophrenia and healthy subjects. Upper column: significant volume differences were detected in the bilateral temporal areas between the healthy subjects and high-risk patients (one-way ANOVA). Middle column: significant volume losses were detected not only in the bilateral temporal area but in the anterior cingulate cortex between the first-episode schizophrenia patients and healthy subjects. Lower column: superposition of upper two results. Yellow showed the difference between the healthy subjects and high-risk patients, green pointed the difference between the first-episode schizophrenia patients and healthy subjects and dark green showed the layered region.

Table 2. White matter DTI measurement in six fibre tracts

		FES ($N = 9$)	pre-onset patients ($N = 10$)	HS ($N = 10$)	F	df	p
LT_ILF	Mean FA	0.40 ± 0.02	0.39 ± 0.02	0.41 ± 0.02	2.75	2	0.082
	Range	0.37–0.44	0.36–0.42	0.38–0.44			
LT_CHP	Mean FA	0.25 ± 0.02	0.25 ± 0.02	0.25 ± 0.02	0.03	2	0.971
	Range	0.22–0.28	0.22–0.28	0.20–0.27			
LT_SLF	Mean FA	0.40 ± 0.02	0.38 ± 0.04	0.43 ± 0.03	5.78	2	0.008*
	Range	0.36–0.43	0.33–0.45	0.39–0.49			
RT_ILF	Mean FA	0.41 ± 0.02	0.41 ± 0.02	0.42 ± 0.02	1.29	2	0.293
	Range	0.39–0.45	0.38–0.43	0.38–0.45			
RT_CHP	Mean FA	0.26 ± 0.02	0.25 ± 0.03	0.26 ± 0.03	0.35	2	0.711
	Range	0.24–0.32	0.21–0.29	0.20–0.31			
RT_SLF	Mean FA	0.44 ± 0.02	0.44 ± 0.03	0.48 ± 0.02	10.31	2	0.001*
	Range	0.43–0.37	0.38–0.47	0.44–0.50			

Post hoc t-test

		p
LT_SLF		
HS	FES	0.048*
	Pre-onset	0.002*
FES	HS	0.048*
	Pre-onset	0.239
Pre-onset	HS	0.002*
	FES	0.239
RT_SLF		
HS	FES	0.002*
	Pre-onset	<0.001*
FES	HS	0.002*
	Pre-onset	0.430
Pre-onset	HS	<0.001*
	FES	0.430

CHP, cingulum hippocampal part; FES, first-episode schizophrenia; HS, healthy subject.
*$p > 0.05$ (correct).

should make it easier to understand the brain changes that will occur as the disease proceeds.

Some schizophrenia studies have shown left temporal impairment (27–29), while others indicate disruptions of the bilateral temporal area (30–32). In addition, a previous study showed that compared with healthy controls, high-risk subjects for schizophrenia showed lower FA in SLF (19). We observed a volume loss in the bilateral temporal cortices and microstructural disturbance in the bilateral SLF. Consistent with the findings of previous studies that used DTI, 3D-T1 weighted volume data and post-mortem brain study, the present study provides direct *in vivo* evidence of structural anomalies in patient groups. Anomalies of temporal regions have found in patients with schizophrenia, and are associates with delusions and hallucinations (33–36). Previous studies showed that the brain change preceded the episode of clinical symptoms (7–11). Our participants at high risk who did not show the delusion and hallucination may develop the precedent morphological change that would affect on the delusion and hallucination. Some neuroimaging studies focussed on the prodromal state have shown temporal lobe anomalies, but the results on the localisation of disturbance were controversial. Some studies have shown left temporal impairment using DTI and volume data (8,10). However, one study indicated reduction of the bilateral temporal grey matter (11), and some papers denied the temporal change using DTI (7,9). These inconsistencies may result from that they used intake criterion for identifying participants at high risk that included so many psychotic symptoms, such as perceptual disturbance, disorganisation, delusion, hallucination and decrease in mental state or functioning. In this study, we regarded the patients who showed perceptual disturbance revealed by the Rorschach test as the high-risk group that fell under the group 1 of the PACE criteria. By using the simple intake criterion, useful information was obtained. Furthermore, structural and functional imaging studies have revealed that the high-risk group is associated with regional volumetric and functional abnormalities that are qualitatively similar to those in patients with schizophrenia but are less severe (37). The present

observations need to be replicated with a larger study population.

In this study, our participants showed the perceptual impairment. The parietal lobe is known to be an essential part of the sensory integration (38), and it could be expected that there were morphological changes of parietal regions in high risk and schizophrenic patients. However, our results did not show the change of parietal region. Previous study that intended the early-onset schizophrenia showed the parietal abnormality (39), though the other studies unlikely show the parietal change (1,3). Previous childhood-onset schizophrenic study suggested that schizophrenic brain change in parietal lobe was obvious in youth, but the changes appear to be diminished with age (40). Our results that did not show the parietal change may be because the mean age of our participants was in the middle of 20s, and the loss of parietal lobe was attenuated.

Functional, anatomical and histopathological studies provide considerable evidence that the connections between subregions of the cingulate cortex and other brain regions are disturbed in schizophrenia (41,42). Previous neuroimaging studies have shown abnormalities of ACC in schizophrenia (43). In this study, the volume loss in ACC was detected not in the high-risk patient group but in the first-episode schizophrenia group. This may result from the fact that the schizophrenic brain shrinkage progress from posterior to anterior (44). Further follow-up studies that focus on the conversion from the prodromal state into schizophrenia are needed to reveal the pattern of ACC shrinkage.

In this study, we evaluated only a few participants. Further work with the large sample size will be necessary to confirm our results.

In summary, the present study confirms that there are proceeding changes in the brains of schizophrenic patients at the pre-onset state. The findings indicate that brain impairments may be altered in patients at the pre-onset of psychosis, possibly as a result of disrupted developmental mechanisms, and, furthermore, that these pathological changes may be predictive of functional outcome. The present observations remain to be replicated with a larger study population and with follow-up of the high-risk patients.

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Psychiatry and Clinical Neurosciences

PCN Frontier Review

Interface between hypothalamic-pituitary-adrenal axis and brain-derived neurotrophic factor in depression

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Although the pathophysiology of depressive disorder remains elusive, two hypothetical frameworks seem to be promising: the involvement of hypothalamic pituitary-adrenal (HPA) axis abnormalities and brain-derived neurotrophic factor (BDNF) in the pathogenesis and in the mechanism of action of antidepressant treatments. In this review, we focused on research based on these two frameworks in relation to depression and related conditions and tried to formulate an integrated theory of the disorder. Hormonal challenge tests, such as the dexamethasone/corticotropin-releasing hormone test, have revealed elevated HPA activity (hypercortisolism) in at least a portion of patients with depression, although growing evidence has suggested that abnormally low HPA axis (hypocortisolism) has also been implicated in a variety of stress-related conditions. Several lines of evidence from postmortem studies, animal studies, blood levels, and genetic studies have suggested that BDNF is involved in the pathogenesis of depression and in the mechanism of action of biological treatments for depression. Considerable evidence has suggested that stress reduces the expression of BDNF and that antidepressant treatments increase it. Moreover, the glucocorticoid receptor interacts with the specific receptor of BDNF, TrkB, and excessive glucocorticoid interferes with BDNF signaling. Altered BDNF function is involved in the structural changes and possibly impaired neurogenesis in the brain of depressed patients. Based on these findings, an integrated schema of the pathological and recovery processes of depression is illustrated.

Key words: hypothalamic-pituitary-adrenal axis (HPA axis), neurotrophic factor, plasticity, stress, TrkB.

MOOD DISORDERS ARE common diseases with a lifetime prevalence of 2–20% for major depression and 0.3–1.5% for bipolar disorder worldwide.[1] In Japan, the 1-year prevalence of major depression was estimated to be as high as 2.9%.[2] Mood disorders also comprise a leading cause of suicide.[3] Depressive disorders are one of the top-ranked diseases in terms of the adjusted life years burden of disease (DALY).[4] Although pathogenesis and pathophysiology of mood disorders remain elusive, two hypothetical frameworks seem to be promising: the involvement of hypothalamic pituitary-adrenal (HPA) axis abnormalities and brain-derived neurotrophic factor (BDNF) in the pathogenesis and in

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the mechanism of action of antidepressants. The former plays an important role in stress response and the latter in structural and functional changes in the brain responsible for mood disorders. In this review, we focused on research based on these two frameworks in relation to mood disorders and tried to formulate an integrated theory of the disorders.

HPA AXIS AND DEPRESSION

Since the seminal work of Selye,[5] a wide variety of stress has been associated with an activation of the hypothalamic-pituitary-adrenal (HPA) axis. Stress-related psychiatric disorders, including major depression, have also been reported to be associated with alteration in HPA axis function. Indeed, abnormality in HPA axis function is one of the most extensively studied biological markers for depression.[6]

HPA axis

Stressors of all sorts, both physical and psychological, activate the HPA axis by increasing the production and release of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) from the paraventricular nucleus of the hypothalamus. Via the portal vein system, CRH, in concert with AVP, stimulates the pituitary to produce adrenocorticotropic hormone (ACTH), which enters the bloodstream and activates the adrenal glands to release glucocorticoids (cortisol in primates, including humans, and corticosterone in rodents). Glucocorticoids, in turn, exert inhibitory feedback effects mainly at the hypothalamus and pituitary glands to inhibit the synthesis and secretion of CRH and ACTH, respectively. Hippocampus also confers an inhibitory effect on HPA axis.

Various measures to monitor HPA axis

In addition to baseline studies, several challenge paradigms have been developed to characterize HPA axis function. These can be divided into psychosocial challenge tests, such as the Trier Social Stress Test (TSST),[7] and pharmacological ones, such as the dexamethasone (DEX) suppression test (DST)[8] and the DEX/CRH test.[9,10]

The TSST, a standardized psychosocial stress test, has been extensively used in the field of psychoneuroendocrinology. This test consists of a 3-min preparation phase followed by a 5-min free speech phase (job interview) and a 5-min mental arithmetic task in front of an audience. In this test the subjects' self-esteem is threatened by a committee that pretends to evaluate the subjects' performance, which leads to the feelings of uncontrollability. A meta-analysis on acute laboratory stressors found the TSST to be a reliable tool to elicit robust physiological stress responses.[11]

To quantify the dysregulation of the HPA axis, the DST, mostly using 1 mg of DEX, has been extensively studied since Carroll *et al.* standardized it as a biological marker for the diagnosis of melancholia.[12] In a series of DST studies, cortisol levels as measured by the DST were shown to be increased in depressed patients.[13] However, it has subsequently become clear that its sensitivity to differentiate depressed patients from healthy controls is not very high,[14,15] and elevated cortisol levels were also observed in non-clinical populations under various stressful conditions.[16,17] The DST has thus failed to fulfill the initial promise as a diagnostic tool for depression. On the other hand, more recent studies that employed DST with lower doses of DEX (e.g. 0.5 mg) have reliably identified enhanced negative feedback in several psychiatric disorders, including post-traumatic stress disorder, chronic fatigue syndrome (CFS) and fibromyalgia.[18–20]

The DEX/CRH test was developed in an attempt to enhance the sensitivity of the DST.[9,10] It is an integrated provocative test for HPA axis function that combines DEX pretreatment with CRH administration on the following day; thus, it is essentially a DST followed by CRH challenge. In the standard protocol of the DEX/CRH test, a relatively high dose (i.e. 1.5 mg) of DEX is used. The merit of this combined test is that at the moment of CRH infusion the HPA axis is downregulated due to negative feedback induced by DEX. This test has been shown to better discriminate depressive patients from healthy people compared to the original DST.[10,21–23] Using the DEX/CRH test, abnormalities in HPA axis function in several other psychiatric disorders, such as bipolar disorder, panic disorder and personality disorders, have also been reported.[24–26] Furthermore, this test, like DST, has been increasingly used to detect the enhanced suppression (or blunted reactivity of cortisol) in varied conditions.

The prednisolone suppression test (PST) is a newly developed pharmacological challenge test to measure HPA axis function.[27] The investigators proposed a test using 5 mg of prednisolone, which gave

approximately 30–40% suppression of salivary cortisol in healthy volunteers, as a useful tool to investigate negative feedback inhibition of the HPA axis. The foundations of this test are the similarities between prednisolone and cortisol in terms of their similar half-lives as well as their similar abilities to bind to and activate both the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR), whereas DEX has a much longer half-life and binds solely to GR. Based on these facts, the authors argue that PST is an ideal test to investigate both enhanced and impaired negative feedback of the HPA axis in patients with psychiatric disorders.[27] A prospective study of patients with depression showed that non-response to inpatient treatment was predicted by a more dysfunctional HPA axis as indicated by higher post-prednisolone cortisol levels.[28] In PST for patients with CFS, significantly greater suppression of both salivary cortisol and urinary cortisol metabolites was observed in CFS patients compared to controls.[29]

HPA axis abnormalities in depression

There is mounting evidence for an important role of HPA axis abnormalities in the pathophysiology of mood disorders.[30] Numerous studies have associated melancholic depression with increased HPA axis activity as revealed, for example, by elevated concentrations of CRH in cerebrospinal fluid, increased volumes of adrenal gland and pituitary, and a higher rate of non-suppression to the DST and the DEX/CRH test.[10,13,31–33] Among depressive disorders, previous DST as well as DEX/CRH studies have observed pronounced HPA axis hyperactivity in psychotic depression.[34,35] Moreover, it is suggested that the DST and the DEX/CRH test could be used as a state-dependent biomarker for depression; in DST studies, conversion from the non-suppressor to suppressor is temporally associated with clinical responses to antidepressants[36,37] and hormonal responses to the DEX/CRH test also tend to restore after successful treatment with antidepressants.[38,39] Using the DEX/CRH test, we examined the HPA axis function in hospitalized depressed patients and found that their cortisol responses were significantly greater than those of healthy controls.[21,22] Such abnormal cortisol responses were improved after inpatient treatment, particularly in those patients who underwent electroconvulsive therapy (ECT) in addition to pharmacotherapy as compared to pharmacotherapy alone (Fig. 1).[22] These results suggested that the DEX/CRH test could serve as a state-dependent marker to monitor HPA axis abnormalities in major depressive episodes. Of particular note, several studies have reported that both in- and outpatients remitted from a major depressive episode who still exhibit exaggerated cortisol responses to the DEX/CRH test are at greater risk for relapse than their counterparts with ameliorated cortisol responses.[40–43]

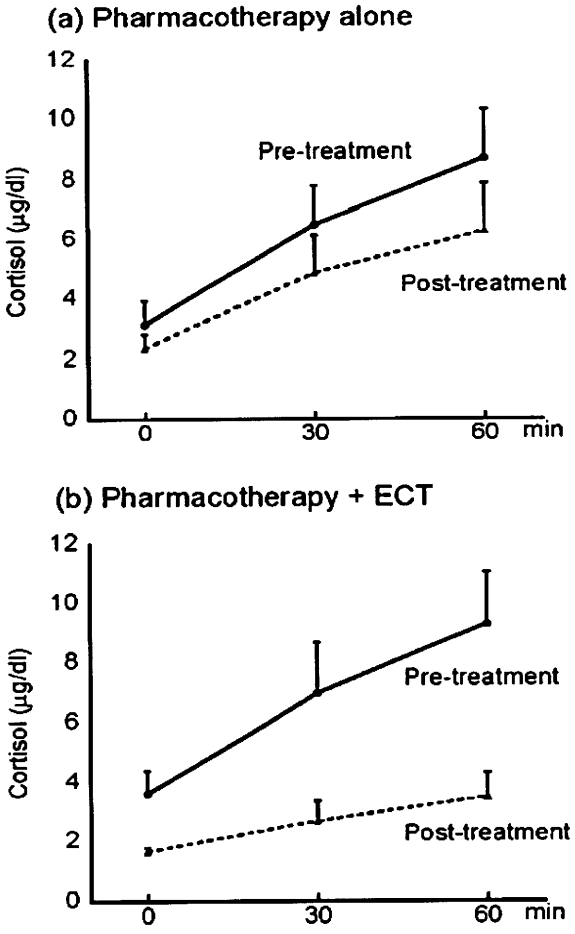

Figure 1. Time-course curves of cortisol responses to the dexamethasone/corticotropin-releasing hormone (CRH) test before and after treatment in (a) the pharmacotherapy group ($n = 23$) and (b) the electroconvulsive therapy (ECT) group ($n = 12$). The *X*-axis represents time after CRH infusion. Error bars represent standard errors of the mean. Adapted from Kunugi *et al.*[22]

In contrast, a number of recent studies using the DEX/CRH test have reported that depressed patients

as a whole show similar,[44–47] or even attenuated, cortisol responses as compared to healthy controls.[48–50] In these studies, patients were one of the following: outpatients,[45–47] chronically depressed patients,[44] depressive patients with psychiatric comorbidity,[50] or long-term sick-leave patients.[48,49] These inconsistent findings on the DEX/CRH test in depressed patients are likely to result from the heterogeneity of depression as well as from a general role of stress in HPA axis function. Indeed, atypical depression, in contrast to melancholic depression, is suggested to relate to hypocortisolism rather than hypercortisolism.[51] Other stress-related psychiatric conditions characterized by hypocortisolism include post-traumatic stress disorder, CFS, and fibromyalgia.[52,53]

BDNF AND DEPRESSION

BDNF function

BDNF belongs to the neurotrophin family, including nerve growth factor (NGF), neurotrophin-3 (NT-3), and NT-4/5, which bind to high-affinity Trk receptors as well as to a common low-affinity p75 receptor. These neurotrophins play important roles in growth, differentiation, maintenance, death/survival, and plasticity of neurons. Interestingly, Trk receptors contain a tyrosine kinase domain that exerts trophic effects, whereas p75 belongs to the tumor necrosis factor family and has a death domain that plays a role in apoptosis as well. Among the neurotrophins, BDNF and its specific receptor TrkB are highly expressed in the adult brain and they are essential in survival of neurons and neurotransmission. In immature neurons, BDNF is involved in growth, differentiation, maturation, and survival, while it plays an important role in synaptic plasticity, augmentation of neurotransmission, and regulation of receptor sensitivity in mature neurons (reviewed in Numakawa *et al.*[54]). BDNF is translated as a precursor protein (proBDNF) and then proteolytically cleaved (processed) to generate a small mature protein (mBDNF). The p75 neurotrophin receptor binds to proneurotrophin with high affinity.[55] BDNF has therefore the yang and yin in the action on neurons depending on processing of proBDNF and differential affinity of proBDNF and mBDNF for TrkB and p75 receptors.[56] Binding of BDNF to TrkB leads to activation of the receptor through phosphorylation, which induces several intracellular signaling pathways, i.e. mitogen-activated protein kinase (MAPK), phospholipase C-gamma (PLCγ), and phosphatidylinositol 3-kinase (PI3K) pathways.[57]

Evidence for BDNF in depression

Studies on postmortem brains of depressed patients and blood levels of BDNF in depressed patients have suggested the important role of BDNF in depression (reviewed in Duman and Monteggia[58]). In postmortem studies of suicide victims with depression, BDNF expression has quite consistently been reported to be reduced in the hippocampus.[59–61] Such reduction was also observed in the prefrontal cortex.[60] Importantly, BDNF expression was unchanged or even increased in the hippocampus of suicide victims with antidepressants,[60,62] which suggests that antidepressants increase the level of BDNF. As regards blood BDNF levels, drug naïve patients with depression often showed decreased BDNF, while they were increased in patients treated with antidepressants (e.g. Shimizu *et al.*[63]). Recent meta-analyses confirmed such findings.[64,65] Further, a significant correlation was found between changes in BDNF level after antidepressant medications and changes in depression scores.[65] However, the possible use of blood BDNF level as a biomarker for depression needs further studies because BDNF exists abundantly in platelets and it is still unclear how the blood level of BDNF reflects that in the brain.

Genetic evidence for BDNF in mood disorders

Growing evidence from molecular genetic studies has also suggested that genetic variations in the BDNF gene confer susceptibility to mood disorders. There are at least two functional polymorphisms in the BDNF gene that have been extensively studied in relation to neuropsychiatric diseases. The most well-studied polymorphism is the single nucleotide polymorphism (SNP) of A758G (rs6265) in the coding region resulting in an amino acid change of Val66Met in the proBDNF protein.[66] Functional characterization of this polymorphism revealed that the Met66 allele was found to be associated with abnormal hippocampal activation and impaired episodic memory in humans.[67] Neurons transfected with Met66-BDNF-GFP showed lower depolarization-induced secretion and the Met66-BDNF-GFP failed to localize to secretary granules or synapses in neurons.

Transgenic mice that were homozygous for the Met66 allele exhibited increased anxiety-related behaviors that were not normalized by the antidepressant, fluoxetine, suggesting that this variant of the BDNF gene may play a role in genetic predispositions to anxiety and depressive disorders.[68] The same research group subsequently reported that the 66Met homozygous mice showed altered adult olfactory bulb neurogenesis with altered spontaneous olfactory discrimination and impaired extinction of conditioned aversive memory.[69,70] Because of these functional effects of the Val66Met polymorphism it was expected that this polymorphism might be associated with susceptibility to various neuropsychiatric diseases. Indeed, bipolar disorder was initially reported to be associated with this polymosphism.[71,72] However, these studies reported that the Val66 allele, which has been shown to be associated with better BDNF functions than the Met allele, was the risk allele for bipolar disorder. Subsequent studies, including ours, could not replicate the association between the Val66 allele and the risk of bipolar disorder.[73,74] As for major depression, a number of association studies have been conducted, yielding inconsistent results. A recent meta-analysis on 14 studies (2812 cases and 10 843 controls) revealed that the Met66 allele (odds ratio [OR] 1.27, 95% confidence interval [CI]: 1.10–1.47) and homozygosity for the Met66 allele (OR: 1.67, 95%CI: 1.19–2.36) gives a risk of major depressive disorder in men but not in women.[75] Interestingly, such a sexually dimorphic effect of the polymorphism was also observed and the Met66 allele was associated with the risk of Alzheimer's disease in female subjects, but not in male subjects.[76] Pertinent to this, BDNF conditional knockout mice, in which the BDNF gene is deleted selectively in the forebrain, demonstrated sexually dimorphic effects in the opposite direction; male conditional knockouts exhibited normal depression-related behaviors, whereas female conditional knockouts displayed a striking increase in depression-like behavior.[77] Indeed, estrogen plays an important role in the expression of BDNF. Estrogen receptors co-localize with BDNF-synthesizing neurons in the forebrain and estrogen induces BDNF expression through the estrogen response element.[78,79]

Another polymorphism of functional significance is the 'BDNF-linked complex polymorphic region (BDNF-LCPR)' located 1kb upstream (putative promoter region) of the coding exon. This polymorphic site was initially reported as a simple dinucleotide repeat (GT repeat).[80] However, we subsequently characterized this polymorphism because previous studies reported a significant association between this repeat polymorphism and bipolar disorder.[71,81] Surprisingly, we found that this polymorphic site has a very complex structure, but not the simple dinucleotide repeat; it contains three different dinucleotide repeats in succession, yielding a total of 23 novel allelic variants.[82] Among the four common alleles, the 'A1 allele' was found to be associated with reduced transcriptional activity and associated with a risk of bipolar disorder, suggesting that this polymorphism confers susceptibility to bipolar disorder by reducing the transcriptional activity of the BDNF gene.[82]

As regards receptors of BDNF, we identified a non-synonymous SNP (Ser205Leu) within the p75 gene; the minor allele (L205) was significantly decreased in the patients than in the controls ($P < 0.05$, OR 0.54, 95%CI 0.31-0.94), suggesting that this allele may have a protective effect against the development of major depression.[83] Furthermore, this association was more strongly observed in patients with a history of attempted suicide than those without such a history. Therefore, the Ser205Leu polymorphism of the p75 gene might be involved in the pathogenesis of depressive disorder and suicidal behavior.

All these findings suggest that genetic variations of BDNF and its receptor p75 play a role in giving susceptibility to mood disorders.

BDNF in the mechanism of action of antidepressants

A number of studies examined the effect of antidepressants on the expression of BDNF. Although some studies have found negative results, the majority of previous studies support the early findings of Nibuya *et al.*, who reported that chronic, not but acute, administration of antidepressants increases BDNF expression in the hippocampus.[84] Several classes of antidepressants, including tricyclics, selective serotonin reuptake inhibitors (SSRI), serotonin noradrenalin reuptake inhibitors (SNRI) and monoamine oxidase inhibitors (MAOI), have been found to increase BDNF in the hippocampus.[58] ECT and other treatments (e.g. repetitive transcranial magnetic stimulation [rTMS]) have also been demonstrated to increase BDNF.[84,85] In relation to diet and nutrition, foods containing omega-3 fatty acid (e.g. fish oil), which has been shown to be effective

in the treatment of major depression,[86] increase BDNF in the hippocampus.[87] Thus, BDNF might be involved in the final common pathway of the various antidepressant treatment strategies. The possible mechanism of increased expression of BDNF by antidepressants is such that chronic antidepressant administration increases the expression of cAMP response element-binding protein (CREB), and CREB, a transcriptional factor, then upregulates its target genes, such as BDNF and TrkB.[88] Furthermore, histone acetylation has also been implicated in the link between antidepressants and increased BDNF expression.[89]

Impacts of stress-induced excessive glucocorticoid on BDNF expression and function

There are at least two lines linking altered HPA axis and BDNF dysfunction. First, stress-induced hyperactivity of the HPA axis and resultant increase in glucocorticoid level reduce the BDNF expression. Second, GR, through which glucocorticoid exerts its effects, directly influences the function of the specific receptor of BDNF, TrkB. Many studies demonstrated reduced expression of BDNF in the hippocampus of animals with various kinds of acute and chronic stress (e.g. restraint, footshock, social isolation, social defeat, swim stress, etc.) and early environmental stress (e.g. maternal deprivation) (summarized by Duman and Monteggia[58]). As mentioned above, stress activates the HPA axis and increases the glucocorticoid level, which in turn decreases BDNF expression in the hippocampus.[90,91] Recent studies suggest that stresses, such as immobilization and social defeat, reduce the expression of BDNF via the mechanism of histone remodeling.[89,92]

Although many studies have shown that stress and glucocorticoid regulates expression of BDNF, there is little information on whether excessive glucocorticoid impacts BDNF function. We then examined the effect of glucocorticoid on BDNF-regulated synaptic function in cultured neurons. In immature hippocampal neurons, exposure to glucocorticoid (DEX) inhibited the BDNF-dependent dendrite outgrowth and synaptic formation (Fig. 2).[93] As a result, BDNF-induced synaptic proteins, such as NR2A, NR2B, GluR1, and synapsin I, were suppressed by DEX, and the inhibitory action of DEX influenced neuronal function even after the neurons had matured.[93] Furthermore, our subsequent study elucidated that GR directly interacts with TrkB and promotes BDNF-triggered PLC-γ signaling for glutamate release via glutamate transporter,[94] which raises the possibility that excessive glucocorticoid might decrease the TrkB-bound GR, which leads to decreased BDNF signaling (Fig. 3). As the observed functional effects of glucocorticoid and GR were not accounted for by altered expression of BDNF, the findings show that stress-induced excess in glucocorticoid impacts not only expression level but also function of the BDNF pathway.

BDNF and structural brain changes in depression

Although there are inconsistencies across studies, a smaller hippocampal volume in depressed patients is thought to be related to the pathophysiology of the disease (reviewed in Eker and Gonul[95]). Many studies in major depressed/suicidal subjects have demonstrated altered brain structure, such as reduction in cell number, density, cell body size, neuronal and glial density in frontal cortical or hippocampal brain areas and decrease in parahippocampal cortex cortical/laminar thickness.[96] There is evidence that antidepressants and ECT increase hippocampal volume in patients with depression.[97,98]

Furthermore, there is evidence that TrkB-dependent neurogenesis is involved in the antidepressant effect; mice lacking TrkB in the hippocampal neuron progenitor cells had impaired neurogenesis and proliferation induced by antidepressant treatment. These mice also demonstrated increased anxiety-like behavior and decreased sensitivity to antidepressants.[99,100] X-irradiation of a restricted region of mouse brain containing the hippocampus prevented the neurogenic and behavioral effects of two classes of antidepressants. These findings suggest that the behavioral effects of chronic antidepressants may be mediated by the stimulation of neurogenesis in the hippocampus.[101]

Taken together, BDNF may play a key role in the brains of recovering patients during antidepressant treatment.[102] However, BDNF might not be the sole key molecule; vascular endothelial growth factor (VEGF), for example, plays an important role in neurogenesis and has been found to be decreased in response to stress and increased by antidepressants and ECT.[103]

As mentioned above, hippocampus regulates the negative feedback of the HPA axis. Therefore, hippocampal damage may lead to disruption of this feed-

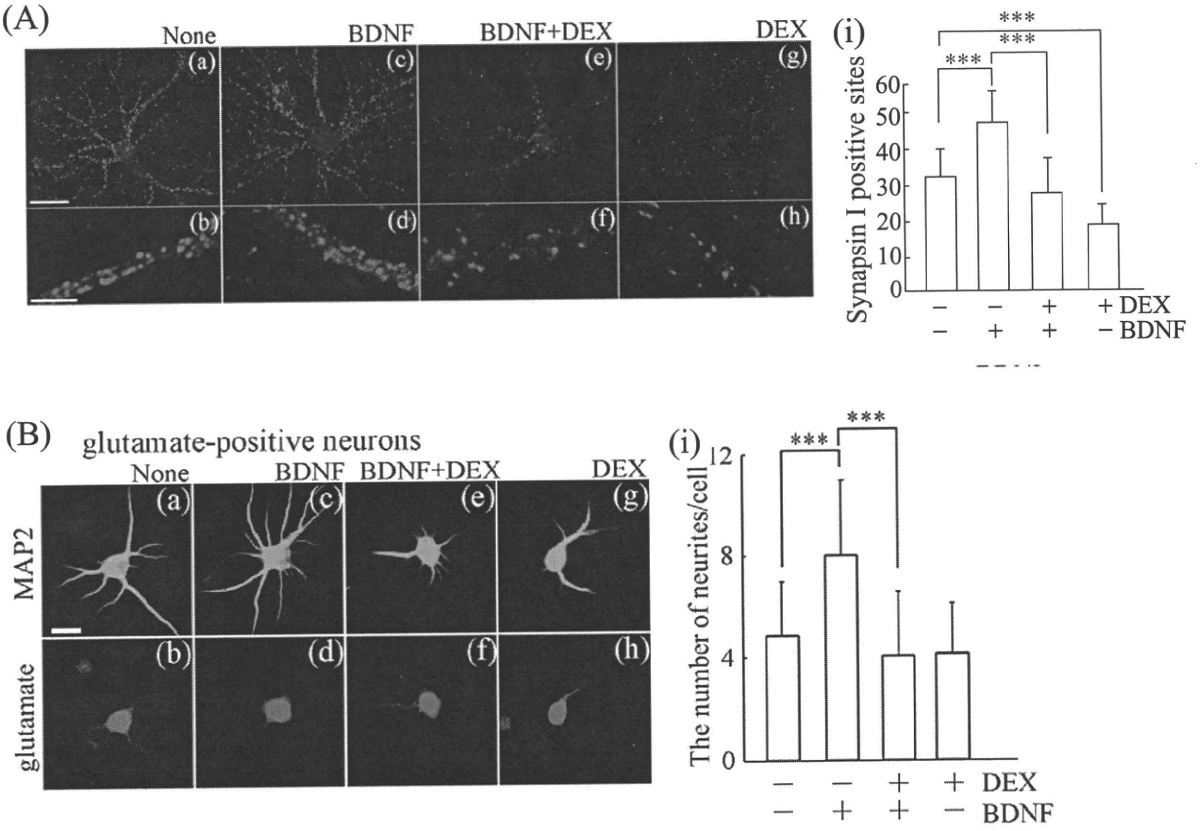

Figure 2. Excessive glucocorticoid (dexamethasone [DEX]) suppresses brain-derived neurotrophic factor (BDNF)-induced neurite outgrowth and synaptic formation in cultured immature hippocampal neurons. (A) The number of presynaptic sites was quantified after immunostaining with anti-synapsin I antibody. Top: Representative images from (a) untreated cultures (none) and (c) cultures pretreated with BDNF, (e) BDNF plus DEX, and (g) DEX. Bar, 20 μm. Bottom: High-magnification images of dendrites from (b) untreated cells (none) and (d) cells pretreated with BDNF, (f) BDNF plus DEX, and (h) DEX. Bar, 10 μm. (i) Quantification of the number of synapsin I-positive presynaptic sites per dendritic shaft (50 μm). Data represent mean ± SD. (B) Effect of DEX on neurite outgrowth of glutamatergic neurons. (a, c, e, and g) MAP2-positive and (b, d, f and h) glutamate-positive glutamatergic neurons are shown (merged images not shown here). (a,b) Untreated cultures (none). (c, d) BDNF increased the number of neurites compared with control, whereas (e,f) DEX significantly suppressed the BDNF-induced neurite outgrowth. (g,h) DEX had no influence compared with control. Bar: 20 μm. (i) Quantification indicates that the number of glutamatergic neurites was increased by BDNF, and the increase was suppressed by DEX. Data represent mean ± SD, $***P < 0.001$; $**P < 0.01$. Adapted from Kumamaru *et al.*[93] with permission.

back loop and resultant continuous hyperactivation of the HPA axis, which in turn further damages the hippocampus. This vicious cycle might be involved in the pathogenesis of depression.

SCHEMA OF DEPRESSION

Based on the roles of the HPA axis and BDNF described above, a possible schema of the pathogenesis and recovery process of depression could be illustrated as in Figure 4. Chronic stress induces hyperactivity of the HPA axis, and resultant excessive stress hormone (glucocorticoid) brings about reduced expression and impaired function of BDNF, which damages the hippocampus and other brain areas. As the hippocampus regulates the feedback system of the HPA axis, its damage further augments the HPA axis activity, which could form a vicious

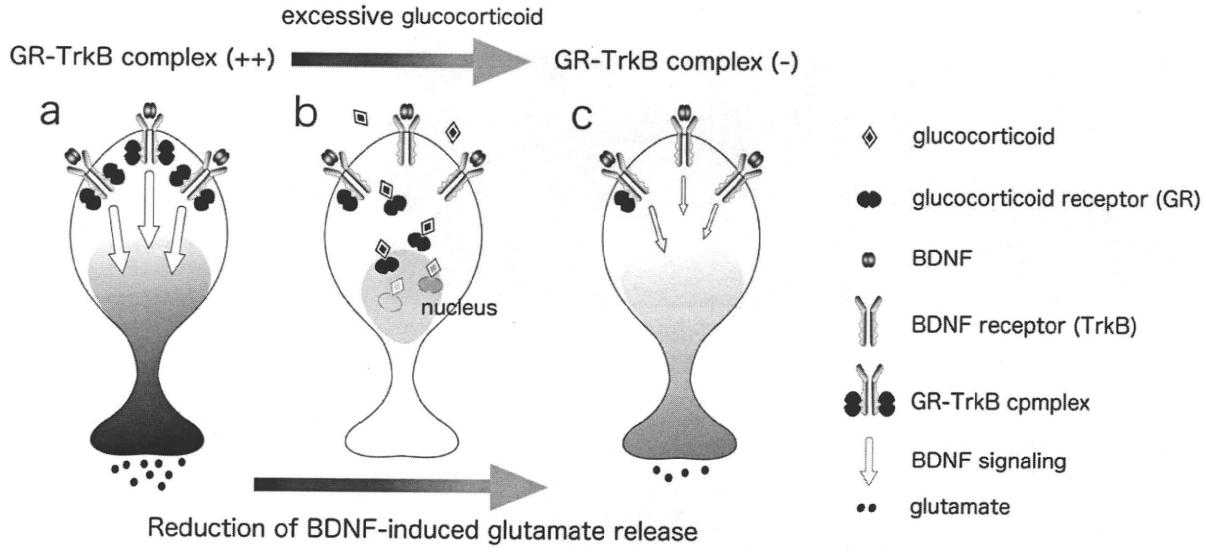

Figure 3. Excessive glucocorticoid might decrease the TrkB-bound glucocorticoid receptor (GR) and decrease brain-derived neurotrophic factor (BDNF) signaling and BDNF-induced glutamate release. (a) When GR-TrkB complex is rich, the BDNF-TrkB signaling for glutamate release is also rich. (b) Exposure to excessive glucocorticoid reduces TrkB-bound GR, which leads to (c) reduced BDNF-TrkB signaling and glutamate release.

cycle. Depressive disorder may develop in the process. In the treatment of depression, relief from stressful situations and biological treatments (e.g. antidepressant medication and ECT) lead to reduction in the hyperactivity of the HPA axis and activation of BDNF and other neurotrophic factors, both of which facilitate each other. Such process will reinstate damaged hippocampus and other brain areas involved in the development of depression.

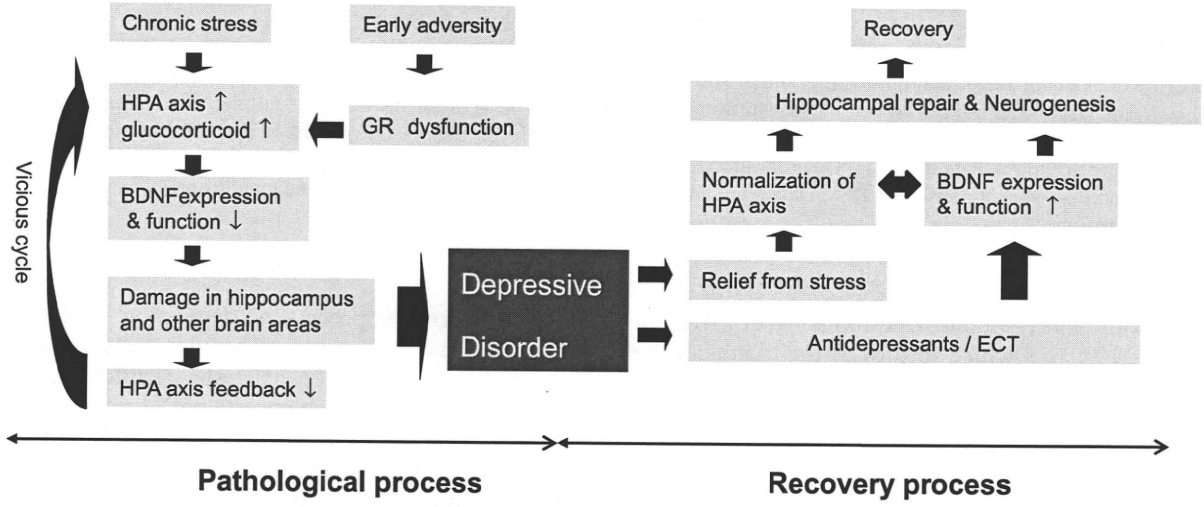

Figure 4. Schematic illustration of pathological and recovery processes of depression focusing on the roles of the hypothalamic pituitary-adrenal (HPA) axis and brain-derived neurotrophic factor (BDNF). ECT, electroconvulsive therapy.

This schema is a rather simplified model and many other factors are likely to be involved. Furthermore, there are some types of depression that clearly do not accord with this schema, atypical depression, for example. As mentioned above, atypical depression has been suggested to be associated with hypoactivity rather than hyperactivity of the HPA axis,[51] and it is relatively resistant to antidepressant treatment. Moreover, there are certain studies that are not always consistent with the BDNF hypothesis in depression.[104] As depression is a heterogenous condition, further studies on the roles of the HPA axis and BDNF in the illness will lead to a valid classification of the illness based on the key molecules.

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