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Hippocampal Astrocytes are Necessary for Antidepressant Treatment of Learned Helplessness Rats

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ABSTRACT: The astrocyte is a major component of the neural network and plays a role in brain function. Previous studies demonstrated changes in the number of astrocytes in depression. In this study, we examined alterations in the number of astrocytes in the learned helplessness (LH) rat, an animal model of depression. The numbers of activated and nonactivated astrocytes in the dentate gyrus (molecular layer, subgranular zone, and hilus), and CA1 and CA3 regions of the hippocampus were significantly increased 2 and 8 days after attainment of LH. Subchronic treatment with imipramine showed a tendency (although not statistically significant) to decrease the LH-induced increment of activated astrocytes in the CA3 region and dentate gyrus. Furthermore, subchronic treatment of naïve rats with imipramine did not alter the numbers of activated and nonactivated astrocytes. However, the antidepressant-like effects of imipramine in the LH paradigm were blocked when fluorocitrate (a reversible inhibitor of astrocyte function) was injected into the dentate gyrus or CA3 region. Injection of fluorocitrate into naive rats failed to induce behavioral deficits in the conditioned avoidance test. These results indicate that astrocytes are responsive to the antidepressant-like effect of imipramine in the dentate gyrus and CA3 region of the hippocampus. © 2010 Wiley-Liss, Inc.

KEY WORDS: learned helplessness (LH); astrocyte; depression; hippocampus; behavior

INTRODUCTION

Depression is related to neuroplasticity, including neurotrophins, cell proliferation, dendritic branching, and synaptogenesis. Neuroplasticity involves the interaction between astrocytes and neurons (Haber et al., 2006). Astrocytes provide trophic support for neurons, neuronal migration, and inflammatory processes for maintenance of the neural network. Thus, astrocytes provide neurons with glutamine for the synthesis of glutamate or γ-aminobutyric acid (GABA) and contribute to the removal of glutamate released during neuronal activity (Willoughby et al., 2003). Astrocytes enhance synaptic activity and promote synaptogenesis (Slezak and Pfrieger, 2003). Astrocytes regulate potassium and calcium during and after stress (Lian and Stringer, 2004). To maintain homeostasis, astrocytes respond to neuroactive compounds including neurotransmitters, neuropeptides, growth factors, cytokines, small molecules, and toxins (Barres et al., 1990; Hosli and Hosli, 1993). Therefore, it is likely that astrocytes play a role in the mechanism of depression.

Postmortem brains of depressed patients demonstrated neuropathological changes in the prefrontal cortex and hippocampus (reviewed by Harrison, 2002). Reductions in the number of astrocytes in the prefrontal cortex (Ongur et al., 1998, Rajkowska et al., 1999, Miguel-Hidalgo et al., 2000, Cotter et al., 2002), amygdala (Bowley et al., 2002), and hippocampus (Müller et al., 2001) in depression were reported. These changes may contribute to the reduction in volume of the hippocampus and dysfunction of neuronal circuits in major depression (reviewed by Rajkowska et al., 1999).

The hippocampus is a candidate site for the impaired functions associated with depression (Duman et al., 1997). It is well documented that patients with depression show a reduction in hippocampal volume (Sheline et al., 1996; Bremner et al., 2000). Among the causes, reduction in hippocampal volume could be due to decreases in neurotrophic factors or neurogenesis (Pezawas et al., 2004; David et al., 2009).

The learned helplessness (LH) paradigm is an animal model of depression (Seligman and Beagley, 1975). In this paradigm, an animal is initially exposed to uncontrollable stress. When the animal is later placed in a situation in which shock is controllable (escapable), the animal has a difficulty in acquiring the escape responses. Thus, LH animals showed increased numbers of escape failures in a two-way conditioned avoidance test. This escape deficit is reversed by chronic antidepressant treatment (Shirayama et al., 2002; Iwata et al., 2006).

In this study, we investigated the role of astrocytes in the hippocampus of LH rats using immunohistochemical methods and behavioral studies. We examined the effects of LH training on the number of activated and nonactivated astrocytes as reflected by the number of glial fibrillary acidic protein (GFAP: a marker of astrocytes) positive cells in the hippocampus. Activated astrocytes are characterized by cellular hypertrophy. Next, we examined the effects of subchronic treatment with imipramine on the number of GFAP-positive cells in the hippocampus of LH rats. Finally, we examined the effects of infusion of fluoro-

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citrate (a reversible inhibitor of astrocyte function) into the hippocampus of LH rats on the antidepressant-like effects of imipramine. Fluorocitrate is uploaded into astrocytes and impairs TCA cycle. We chose the dose and time course of fluorocitrate injection on a basis of a previous study demonstrating that astrocyte almost recovered at 24 h after injection of fluorocitrate and high concentration of fluorocitrate has a possibility to cause irreversible damage to astrocyte (Paulsen et al., 1987).

MATERIALS AND METHODS

Animal and Treatments

Animals-use procedures were in accordance with the Tottori University Guide for the Care and Use of Laboratory Animals and were approved by the Tottori University Animal Care and Use Committee. Male Sprague Dawley rats (250–300 g) were used. The animals were housed under a 12 h light/dark cycle with free access to food and water.

Fluorocitrate was dissolved in 0.1 M HCl, precipitated by addition of a few drops of 0.1 M Na_2SO_4, then buffered with 0.1 M Na_2HPO_4 and centrifuged at 1,000*g* for 5 min, and the supernatant was diluted with 0.9% saline.

Learned Helplessness Paradigm

LH behavioral tests were performed using the Gemini Avoidance System (San Diego, CA). This apparatus has two compartments divided by a retractable door. On days 1 and 2, rats were subjected to 60 inescapable electric foot shocks (0.65 mA, 30 s duration, averaging 20–40 s). On day 3, a two-way conditioned avoidance test was performed as a post-shock test to determine if the rats showed the predicted escape deficits. This screening session consisted of 30 trials in which electric foot shocks (0.65 mA, 6 s duration, at random intervals [mean of 30 s]) was preceded by a 3 s conditioned stimulus tone that remained on until the shock was terminated. Rats with more than 20 escape failures in the 30 trials were regarded as having reached criterion. Approximately 65% of the rats reached this criterion. For antidepressant treatment, LH rats or naïve rats were treated with imipramine (20 mg/kg, i.p., once daily) or saline for 7 days (from day 4 to day 10).

Rats were anesthetized with pentobarbital sodium solution (50 mg/kg, intraperitoneal injection, Abbott Laboratories) and surgery was performed using a stereotaxic apparatus (Narishige, Tokyo). Rats received bilateral microinjection of fluorocitrate (0.1 or 0.5 nmol/side) or 0.9% saline on day 4 and day 7 (two times, first and forth days during antidepressant treatment for 7 days) because disruption of astroglial metabolism by fluorocitrate lasts for more than 24 h (Paulsen et al., 1987). A total volume of 1.0 μl was infused into each side of hippocampal regions over 15 min and the injection syringe was left in place for an additional 5 min to allow for diffusion. The coordinates for the dentate gyrus (DG) and CA3 relative to the bregma according to the atlas of Paxinos and Watson (1997) were as follows: −3.8 anteroposterior (AP), ±2.0 lateral, −3.2 dorsoventral (DV) from dura (DG); and −3.6 AP, ±3.8 lateral, −3.0 DV from dura (CA3). The placements of injection cannula in the hippocampus are shown in Figure 1. On day 11, a two-way conditioned avoidance test was performed.

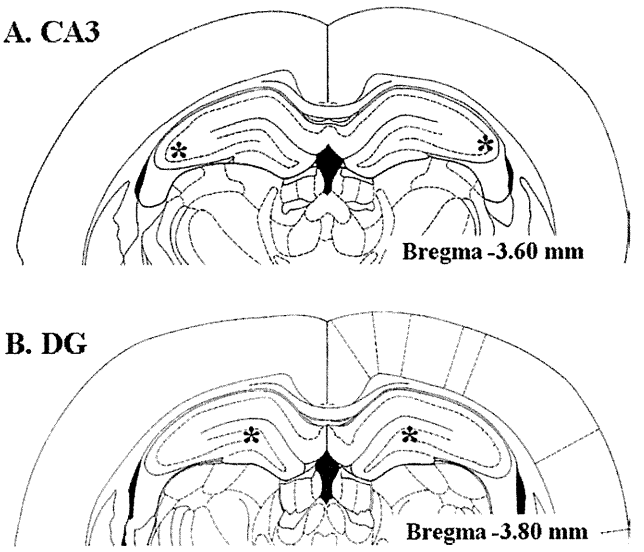

FIGURE 1. A schematic representation of microinjection sites within the CA3 region of hippocampus (A) and the dentate gyrus of hippocampus (B).

Immunohistochemistry

We performed three experimental procedures. In one, rats were killed two days after the acquisition of LH (Experiment 1). Next, LH rats were killed 24 h after subchronic treatment with imipramine for 7 days (Experiment 2). In addition, naïve rats were killed 24 h after subchronic treatment with imipramine for 7 days (Experiment 3).

All rats were placed under deep pentobarbital anesthesia (50 mg/kg, i.p.) and killed via intracardial perfusion with 4% paraformaldehyde in 0.1 M PBS, pH 7.4. Brains were removed, postfixed overnight in the same fixative at 4°C, and stored at 4°C in 30% sucrose. Serial coronal sections of the brains were cut (35 μm sections) on a Microslicer® (DTK-1000, Dosaka EM, Kyoto, Japan), and sections were stored at 4°C in 0.1 M PBS containing 0.1% sodium azide.

GFAP immunohistochemistry was investigated as described below. Free-floating sections were washed three times for 5 min in 0.1 M PBS and then incubated for 10 min in 0.1 M PBS containing 0.6% hydrogen peroxide to eliminate endogenous peroxidases. After washing three times for 5 min in 0.1 M PBS, sections were then incubated for 1 h in 0.1 M PBS containing 2% bovine serum albumin (BSA), 5% normal goat serum, and 0.2% Triton X-100 for blocking. For GFAP immunostaining, a primary GFAP mouse monoclonal antibody (1:1,000; Chemicon, Temecula, CA) was used. The secondary antibody was biotinylated horse antimouse (Vector Laboratories, Burlingame, CA). Amplification was done with an avidin-

biotin complex (Vectastain Elite ABC kit; Vector Laboratories) and was visualized with DAB (Vector Laboratories).

Three slices of the same region of the hippocampus were selected, and the number of GFAP-positive astrocytes per square on both sides (6 sites) was counted. Star-shaped astrocytes were visualized by GFAP immunostaining in the dentate gyrus (molecular layer, subgranular zone, and hilus), and CA3 and CA1 regions of the hippocampus (Fig. 2). Astrocytes were classified as activated or nonactivated astrocytes by measuring the size of the cell body, and the length and thickness of the dendrites was calculated (Fig. 3). Reactive astrocytes are recognized by GFAP labeling and extended lengths of processes (Viola et al., 2009). We differentiated activated astrocytes from nonactivated astrocytes mainly by dimension rather than by length of longest process. The numbers of activated astrocytes and the combined activated and nonactivated astrocytes were counted.

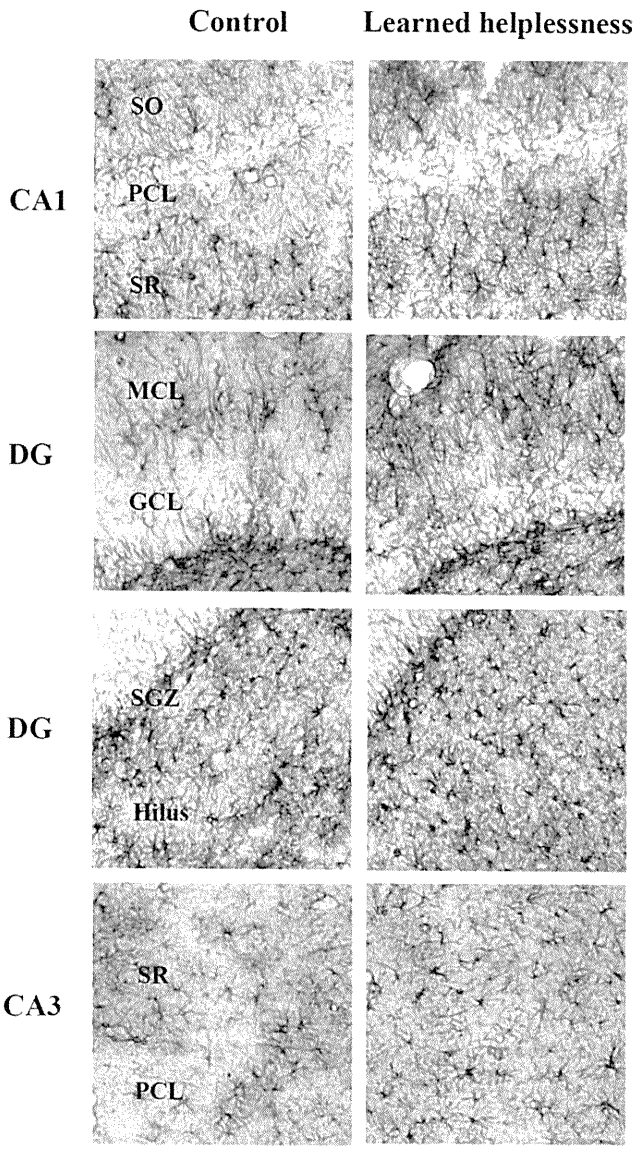

FIGURE 2. GFAP immunostaining in the hippocampus. GCL, granule cell layer; ML, molecular layer; PCL, pyramidal cell layer; SGZ, subgranular zone; SR, stratum radiatum; SO, stratum oriens.

Date Analysis

Statistical differences among more than three groups were estimated by a one-way ANOVA, followed by Scheffe's test. For comparison of the mean values between the two groups, statistical evaluation was done using the two-tailed Student's *t*-test. The criterion of significance was $P < 0.05$.

RESULTS

Increased Number of Activated Astrocytes after Attainment of LH and Attenuating Effects of Imipramine

The numbers of activated astrocytes were significantly increased in the CA1, molecular layer, subgranular zone, hilus, and CA3 regions 2 and 8 days after the attainment of LH (Fig. 4). The magnitude of the change in the number of activated astrocytes was bigger 8 days after the attainment of LH than 2 days after (Fig. 4). However, subchronic treatment with imipramine showed a tendency (although not statistically significant) to decrease the LH-induced increment rate of activated astrocytes at the subgranular zone ($P = 0.054$), hilus ($P = 0.085$), and CA3 region ($P = 0.074$). Furthermore, subchronic treatment of naïve rats with imipramine did not alter the numbers of activated astrocytes in the regions examined (Fig. 4).

Combined Numbers of Activated and Nonactivated Astrocytes After Attainment of LH and Effects of Imipramine

Significant increases in the total numbers of both activated and nonactivated astrocytes were found in the CA1 and CA3 regions, but not in the molecular layer, subgranular zone, and hilus two days after the attainment of LH (Fig. 5). The total numbers of both activated and nonactivated astrocytes were significantly increased in all regions examined 8 days after the attainment of LH (Fig. 5). Furthermore, subchronic treatment with imipramine did not alter the combined numbers of either activated or nonactivated astrocytes in LH rats (Fig. 5). Additionally, subchronic treatment of naïve rats with imipramine did not alter the total numbers of activated or nonactivated astrocytes in the regions examined (Fig. 5).

Effects of Inhibition of Hippocampal Astrocyte Function of LH Rats on Conditioned Avoidance Test

The antidepressant-like effects of imipramine were significantly blocked in the LH paradigm when fluorocitrate was injected into the dentate gyrus (Fig. 6). Similarly, the antide-

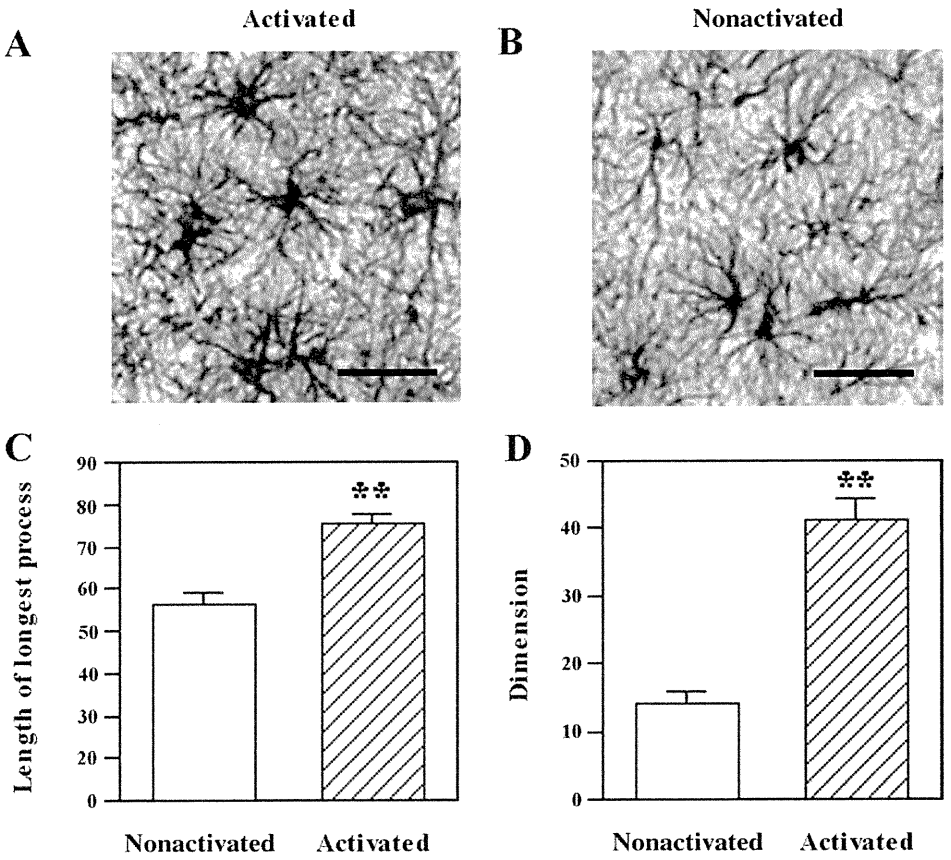

FIGURE 3. Representative images of GFAP immunoreactive activated (A) and nonactivated (B) astrocytes. Scale bar: 25 μm. The lengths of the longest processes (C) and dimensions (D) of activated and nonactivated astrocytes are indicated. The results are expressed as mean ± SEM. Sample number = 10. $^{**}P < 0.01$ when compared with controls (Student's *t*-test).

pressant-like effects of imipramine were significantly blocked when fluorocitrate was injected into the CA3 region of the hippocampus (Fig. 7). Meanwhile, injection of fluorocitrate into the dentate gurus or CA3 region of naïve rats failed to induce behavioral deficits in the conditioned avoidance test (Figs. 6 and 7).

DISCUSSION

The main finding of this study was that the numbers of activated astrocytes and the combined numbers of activated and nonactivated astrocytes were increased in the regions examined 2 and 8 days after the attainment of LH. Thus, LH continued to activate and induce astrocytes. This result was in a good agreement with previous studies. For example, repeated immobilization stress increased αB-crystallin, which is localized in astrocytes and increases in reactive astrocytes, in the hippocampus through activation of astroglia (Yun et al., 2002). Chronic restraint stress increased glia-specific excitatory amino acid transporter (GLT-1) in the dentate gyrus and CA3 region of the hippocampus (Reagan et al., 2004). Subchronic treatment of amphetamine, which induces not only pleasure but also stress, including supersensitivity, increased GFAP levels in the rat hippocampus (Frey et al., 2006). Chronic unpredictable stress increased levels of immunoreactivity of GFAP in the ventral tegmental area (Ortiz et al., 1996). Therefore, the LH condition and repeated stress produce similar glial changes in the brain.

The prevailing view about the response of astrocytes to injury is that the appearance of reactive astrocytes impedes the regenerative process of scar tissue formation. Therefore, the increases in the numbers of activated and nonactivated astrocytes 2 and 8 days after the attainment of LH are associated with impairments in neuronal function, which may be the cause of LH. However, it is likely that astrocytes play a role in neuroprotection and the regenerative process after neuronal impairment (Eddleston and Mucke, 1993). Cytokine-stimulated astrocytes promoted the recovery of CNS function (Liberto et al., 2004). Thus, the LH paradigm induced increases in the number of activated and nonactivated astrocytes, which could be a compensatory response to stress. In support of this, environmental enrichment, which increases

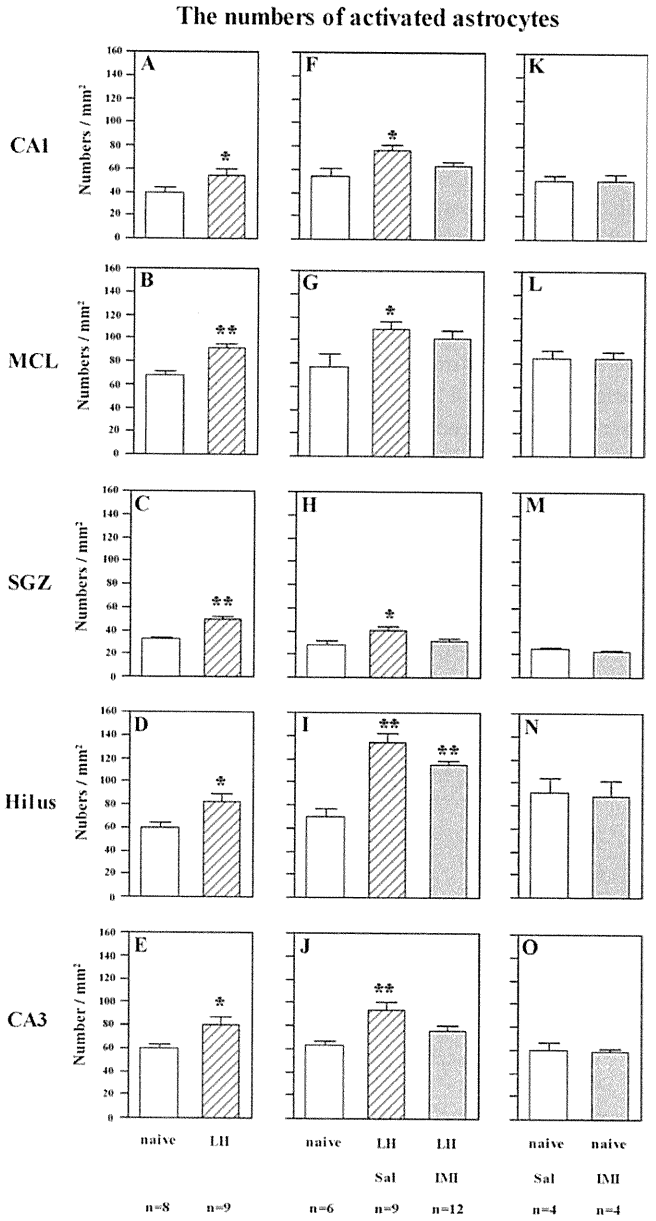

FIGURE 4. The number of activated astrocytes in the CA1, granule cell layer, hilus and CA3 regions of hippocampus of LH rats and effect of antidepressant drug. (A) $t = 2.145$, $P = 0.0487$; (B) $t = 4.618$, $P = 0.0003$; (C) $t = 5.360$, $P = 0.0001$; (D) $t = 2.661$, $P = 0.0178$; (E) $t = 2.55$, $P = 0.0222$; (F) $F(2,24) = 4.821$, $P = 0.0174$; (G) $F(2,24) = 3.732$, $P = 0.0388$; (H) $F(2,24) = 5.292$, $P = 0.0125$; (I) $F(2,24) = 23.26$, $P < 0.0001$; (J) $F(2,24) = 6.190$, $P = 0.0068$. (K) $t < 0.001$, $P > 0.9999$; (L) $t = 0.29$, $P = 0.9775$; (M) $t = 1.243$, $P = 0.2603$; (N) $t = 0.171$, $P = 0.8696$; (O) $t = 0.234$, $P = 0.8225$. $^{*}P < 0.05$; $^{**}P < 0.01$ when compared with controls (Student's t-test or ANOVA followed by Scheffe's test).

neurogenesis in the hippocampus, produced an increase in the ramification of astrocytic processes and the number and length of primary processes extending in the hippocampus (Viola et al., 2009). Furthermore, an increase in the number of GFAP-labeled astrocytes was seen in the cingulate of postpartum rats (Salmaso et al., 2009). Therefore, an alternative explanation may be that neuroplasticity including nerve growth, neuroprotection, and regeneration requires astrocytes.

However, other animal studies showed contrasting results. For example, a significant deficit in GFAP-immunoreactive cells was found in the prefrontal cortex, amygdala, and hippocampus in the Wistar-Kyoto rat strain (a model of depression)

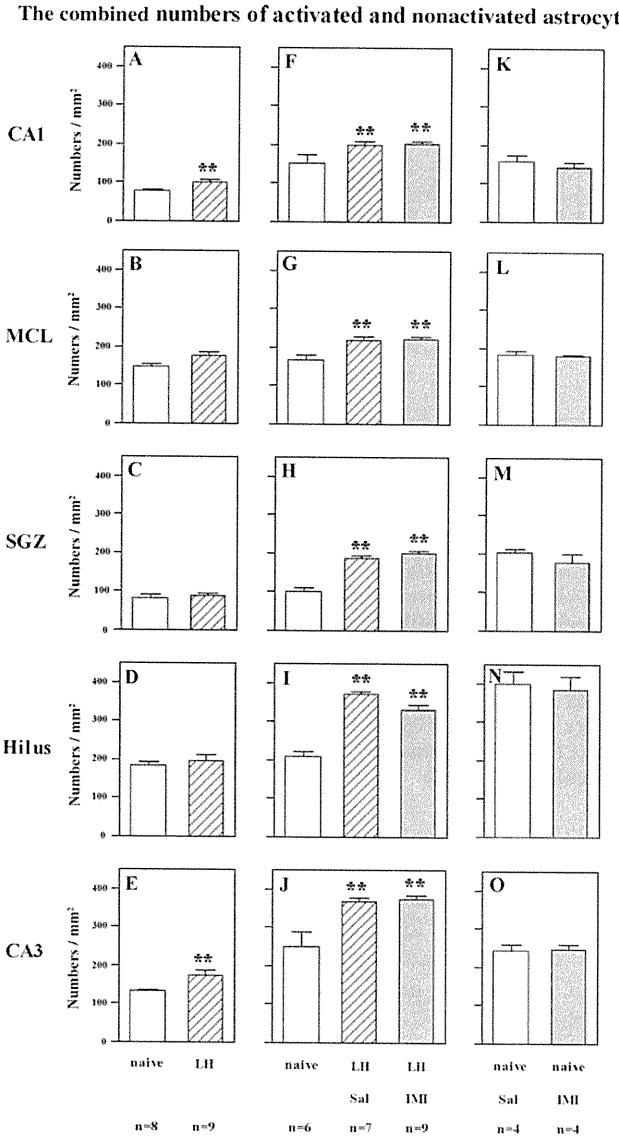

FIGURE 5. The combined number of both activated and non-activated astrocytes in the CA1, granular cell layer, hilus and CA3 regions of the hippocampus of LH rats and effects of antidepressant drug. (A) $t = 3.769$, $P = 0.0019$; (B) $t = 2.090$, $P = 0.0541$; (C) $t = 0.823$, $P = 0.4236$; (D) $t = 0.610$, $P = 0.5508$; (E) $t = 3.447$, $P = 0.0036$; (F) $F(2,24) = 5.541$, $P = 0.0105$; (G) $F(2,24) = 4.042$, $P = 0.0307$; (H) $F(2,24) = 42.545$, $P < 0.0001$; (I) $F(2,24) = 45.749$, $P < 0.0001$; (J) $F(2,24) = 13.822$, $P = 0.0001$. (K) $t = 0.646$, $P = 0.5422$; (L) $t = 0.410$, $P = 0.6940$; (M) $t = 1.014$, $P = 0.3498$; (N) $t = 0.314$, $P = 0.7643$; (O): $t = 0.149$, $P = 0.8864$. $^{*}P < 0.05$; $^{**}P < 0.01$ when compared with controls (Student's t-test or ANOVA followed by Scheffe's test).

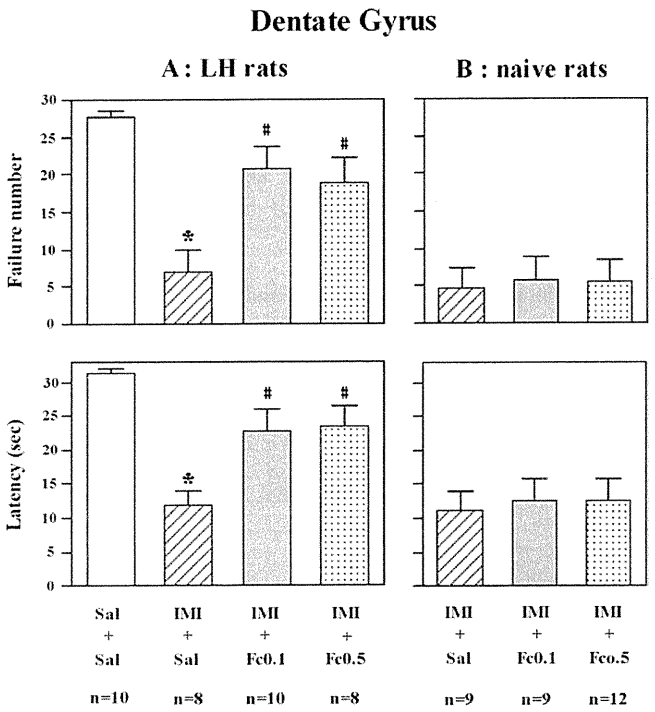

FIGURE 6. Effects of injection of fluorocitrate into the DG of the hippocampus of LH rats receiving imipramine in the conditioned avoidance test. Escape failure number and latency to escape were determined. The results are expressed as mean ± SEM. Shown on the right are the results of fluorocitrate-injection into imipramine-treated normal rats for comparison. Left top, $F(3,32) = 10.554$, $P < 0.0001$; left bottom, $F(3,32) = 10.140$, $P < 0.0001$; right top, $F(2,27) = 0.212$, $P = 0.8104$; right bottom, $F(2,27) = 0.060$, $P = 0.9415$. $^{*}P < 0.05$ when compared with controls (saline+saline-treated LH rats) (ANOVA followed by Scheffe's test). $^{\#}P < 0.05$ when compared with imipramine-treated LH rats (ANOVA followed by Scheffe's test). Fc, fluorocitrate; IMI, imipramine; Sal, saline

(Gosselin et al., 2009). Chronic psychosocial stress decreased both the number and somal volume of astroglia in the hippocampus (Czéh et al., 2006). Furthermore, glial loss in the prefrontal cortex induced depressive-like behaviors (Banasr and Duman, 2008). The precise function of astrocytes needs to be established.

The above discrepancy could be explained by Selye's definition of stress as a response to any demand that produces three stages (alarm, resistance and exhaustion). Our working hypothesis is that astrocytes first respond to alarm, and then become activated, or new astrocytes are induced to increase the numbers at the stage of resistance, and finally astrocytes tire and the numbers of astrocytes decrease at the stage of exhaustion. The increase in the numbers of activated and nonactivated astrocytes in the present study could be considered as a resistant and compensatory mechanism, which is distinct from the final reduction in the number of astrocytes, although this is speculation. Further studies are needed to elucidate this hypothesis.

The next finding is that the reversible impairment of astrocyte function by infusion of fluorocitrate into the dentate gyrus or CA3 region of LH rats blocked the antidepressant-like effects of subchronic treatment with imipramine on the conditioned active avoidance test. Fluorocitrate specifically and reversibly disrupts astroglial metabolism by blocking aconitase, an enzyme integral to the TCA cycle (Paulsen et al., 1987; Hassel et al., 1994; Willoughby et al., 2003). We can assume various mechanisms. First, there is a possibility that the blockade of glutamate uptake and glutamine synthesis lead increased extracellular glutamate levels and decreased extracellular glutamine levels, interrupting the antidepressant effect of imipramine. In support, treatment with antidepressants reduced the serum levels of glutamate, and increased the serum levels of glutamine in major depression patients (Maes et al., 1998). Future study will be needed to elucidate the mechanism of glutamine in the effects of antidepressants. Second, the impairment of astrocytes may increase extracellular serotonin levels like antidepressant drugs because antidepressant drugs inhibit a glial serotonin transporter in the rat brain, increasing extracellular serotonin levels (Bel et al., 1997). It is likely that increases in extracellular serotonin levels remind us of selective serotonin reuptake inhibitor (SSRI) type of antidepressants. However, the present study demonstrated that inhibi-

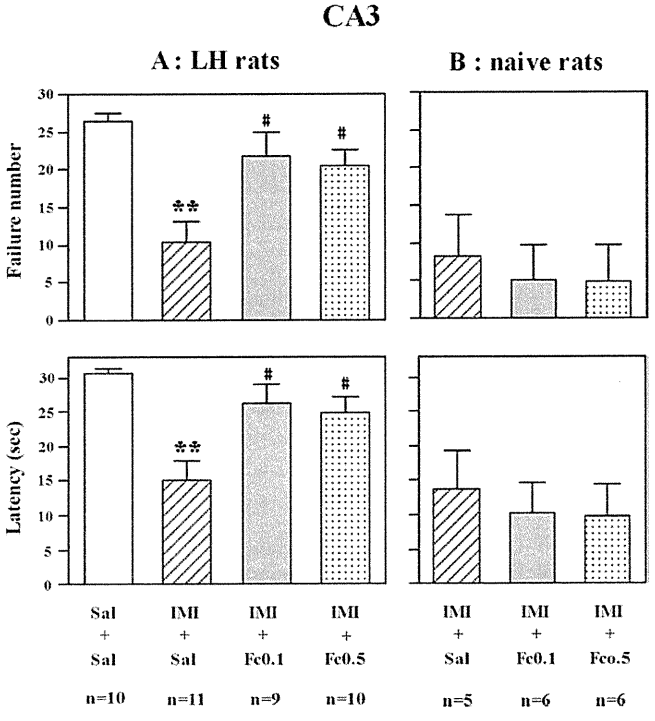

FIGURE 7. Effects of injection of fluorocitrate into the CA3 region of the hippocampus of LH rats receiving imipramine on conditioned avoidance test. Escape failure number and latency to escape were determined. The results are expressed as mean ± SEM. Shown on the right are the results of fluorocitrate-injection into imipramine-treated normal rats for comparison. Left top, $F(3,32) = 10.140$, $P < 0.0001$; left bottom, $F(3,32)$, $P < 0.0001$; right top, $F(2,14) = 0.132$, $P = 0.8778$; right bottom $F(2,14) = 0.199$, $P = 0.8222$. $^{**}P < 0.01$ when compared with controls (saline+saline-treated LH rats) (ANOVA followed by Scheffe's test). $^{\#}P < 0.05$ when compared with imipramine-treated controls (ANOVA followed by Scheffe's test). Fc, fluorocitrate; IMI, imipramine; Sal, saline.

tion of astrocytes function blocks the beneficial effects of antidepressant drugs on the LH paradigm. Thus, serotonin would be irrelevant for the effects of fluorocitrate. Finally, astrocytes secrete physiologically active agents including brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) (Chen et al., 2006). It is well documented that infusion of BDNF into the hippocampus produced antidepressant-like effects (Shirayama et al., 2002) and that antidepressants treatment increased GDNF mRNA and GDNF release, promoting neuronal survival and protection from the damaging effects of stress (Hisaoka et al., 2001). Meanwhile, L-deprenyl, an inhibitor of monoamine oxidase B, which is predominantly localized in astrocytes, potentiates the reaction of astrocytes to mechanical lesions, and increases basic fibroblast growth factor (bFGF) production (Biagini et al., 1994). Furthermore, intracerebroventricular administration of FGF2 exerted antidepressant-like effects (Turner et al., 2008). Taken together, BDNF, GDNF, and FGF could play an important role in antidepressant effects of imipramine. Future study needs to elucidate the relationships of antidepressant drugs with glutamine, BDNF, GDNF, and FGF in astrocytes.

In conclusion, the numbers of activated and nonactivated astrocytes were significantly increased in the hippocampus after the attainment of LH. Subchronic treatment with imipramine showed a tendency (although not statistically significant) to decrease the numbers of activated astrocytes at the subgranular zone, hilus, and CA3 region. However, subchronic treatment of naïve rats with imipramine failed to induce changes in the numbers of astrocytes. Finally, the antidepressant-like effects of imipramine were significantly blocked in the LH paradigm when fluorocitrate was injected into the dentate gurus or CA3 region, whereas injection of fluorocitrate into naive rats failed to induce behavioral deficits in the conditioned avoidance test. These results suggest that hippocampal astrocytes contribute to the pathophysiology of depression.

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The pilot study of a Neuropsychological Educational Approach to Cognitive Remediation for patients with schizophrenia in Japan

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ABSTRACT

The main aim of this study is to demonstrate the feasibility and efficacy of a Neuropsychological Educational Approach to Cognitive Remediation (NEAR) in Japan. This multi-site study used a quasi-experimental design. Fifty-one patients with schizophrenia or schizoaffective disorder participated. The NEAR program consisted of two 1-h computer sessions per week and an additional group meeting session lasting 30 to 60 min once a week. The subjects completed 6 months of NEAR sessions before being assessed. Moreover, taking into consideration the possible practice effect, we assessed 21 control patients twice with an interval of 6 months. We assessed cognitive function by using the Japanese version of the Brief Assessment of Cognition in Schizophrenia (BACS-J). Consequently, the NEAR group showed significant improvement in overall cognitive function, and in comparison with the control group, these findings were generally similar except for motor speed. Although the present study has its limitations, it demonstrates that the NEAR is feasible in Japan as well as it is in Western countries.

1. Introduction

It is widely accepted that cognitive dysfunction in schizophrenia plays a major role in determining social function (Green et al., 2000). Although there have been numerous reports that indicate the effectiveness of atypical antipsychotics (AAPs) on cognitive function, the size of the effect of AAPs is generally about 0.2–0.5 standard deviations (S.D.) (Woodward et al., 2005; Keefe et al., 2007), while the extent of cognitive dysfunction in schizophrenia is about 1–1.5 S.D. below the level of healthy populations (Bilder et al., 2000; Heinrichs, 2004). To bridge this gap, other treatment methods, such as cognitive remediation, have been considered in Western countries.

In Japan, the "Services and Supports for Persons with Disabilities Act" was established in 2006. Although disabled persons' employment, deinstitutionalization, and socialization were promoted by this law, there are actually many people with psychiatric illnesses, including patients with schizophrenia, who still suffer from social dysfunction. With the aim of alleviating the many difficulties that patients encounter in their lives, cognitive remediation therapy for patients with schizophrenia has gradually been launched in Japan (Nemoto et al., 2009).

We have become interested in one of the cognitive remediation therapies, namely, a Neuropsychological Educational Approach to Cognitive Remediation (NEAR) (Medalia and Freilich, 2008; Medalia et al., 2009), which is theoretically based on neuropsychology, educational psychology, learning theory, and cognitive psychology. After participating in 1-week clinician training for NEAR, we started implementing NEAR in Japan. NEAR is an evidence-based approach to cognitive remediation specifically developed for use with psychiatric patients. NEAR is a group-based treatment that provides a positive learning experience to each and every client, to promote independent learning, and to promote optimal cognitive function in everyday life. Sessions are structured in a way to enhance intrinsic motivation and learning. The main aim of this study is to demonstrate the feasibility and efficacy of NEAR in Japan by assessing its effectiveness on cognitive function using neuropsychological indices as a primary endpoint.

2. Methods

This multi-site study used a quasi-experimental design. All participants were recruited from five psychiatric hospitals in the western region of Japan called the 'San-in' district and exposed to NEAR in each hospital. All participants were recruited on the basis of consecutive referrals.

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Table 1
Baseline demographic variables.

	NEAR group	Control group
Number of patients		
Sch: Schizophrenia	Sch: 48	Sch: 21
SchAf: Schizoaffective disorder	SchAf: 3	SchAf: 1
Gender	Male: 31, Female: 20	Male: 14, Female: 8
Mean age	36.1 ± 10.6 y.o.	41.1 ± 12.4 y.o.
Years of education	13.5 ± 2.5 years	12.5 ± 2.6 years
Duration of illness	13.8 ± 9.8 years	16.1 ± 10.8 years
Age at onset of illness	22.3 ± 6.6 y.o.	22.6 ± 6.3 y.o.
Total number of hospitalizations	2.8 ± 3.1 times	4.6 ± 5.2 times
Total months of hospitalization	19.4 ± 29.4 Months	39.3 ± 65.8 months
Mean dosage of antipsychotics (Chlorpromazine equivalent dose)	634.5 ± 364.9 mg/day	699.2 ± 569.2 mg/day
Treatment settings (Outpatient or inpatient) *	Outpatients: 42 Inpatients: 9	Outpatients: 12 Inpatients: 10
NEAR attendance rate	0.90 ± 0.11	
BACS-J z score; Verbal memory**	−1.09 ± 0.92	−2.00 ± 1.05
BACS-J z score; Working memory	−0.95 ± 0.95	−1.30 ± 1.08
BACS-J z score; Speed	−1.60 ± 1.37	−2.25 ± 1.74
BACS-J z score; Verbal fluency	−0.47 ± 1.00	−0.71 ± 0.89
BACS-J z score; Attention and speed of information processing	−1.24 ± 0.88	−1.56 ± 0.77
BACS-J z score; Executive function	−0.57 ± 1.42	−1.56 ± 2.15
[EX]**	−0.79 ± 0.59	−1.10 ± 0.59
BACS-J composite score**	−1.65 ± 1.27	−2.61 ± 1.51

* $p<0.05$ Fisher's exact test.
** $p<0.05$ Student's t test.
[EX] = −log[2 − (Executive function BACS-J z score)].

2.1. Subjects (Table 1)

After a complete explanation of the study, informed consent was obtained from the participants. The protocol of this study was approved by the Ethics Committee of Tottori University. Inclusion criteria were outpatients or inpatients (a) with a diagnosis of schizophrenia or schizoaffective disorder made by two experienced psychiatrists according to DSM-IV-TR criteria, (b) between 13 and 65 years old, (c) able to sit for a 1-hour session, (d) willing to participate in the study, and (e) being recommended by their doctors. Exclusion criteria were patients (a) with active substance or alcohol abuse or having left a detoxification program within the last month, or (b) with traumatic head injury within the past 3 years.

Sixty-two patients were referred to the program, and 11 dropped out at the midway point (the dropout rate was 17.4%). Among these 11 patients, five patients dropped out owing to a lack of motivation and five patients dropped out because of relapse of psychotic symptoms. One patient found a job and left the program. Six of the patients who withdrew left the program within the first half of the 6-month trial. Finally, 51 patients with schizophrenia or schizoaffective disorder completed the NEAR program. The NEAR program consisted of two 1-h computer sessions per week and an additional group meeting session lasting 30 to 60 min once a week. The subjects completed approximately 6 months before the program's efficacy was assessed.

Moreover, we assessed 22 control patients twice with an interval of 6 months, taking into consideration a possible practice effect, which may have affected the scores of neuropsychological tests. They did not receive any cognitive training program including NEAR. As for the clinical backgrounds, the treatment settings were significantly different between the two groups, with more inpatients being included in the control group than in the NEAR participant group.

In each computer session, patients engaged with some educational computer software that was related to various domains of cognitive function, including attention, memory, and executive function, taking into account the profiles of the patients' cognitive impairments. The software available in Japan is not identical to that in Western countries; however, it appeared to cover the relevant cognitive domains (Table 2).

The main aim of the group meeting sessions was to contextualize the computer training into the patients' everyday activities. The process should lead to enhancing motivation and generalization of cognitive skills to real-life activities.

One of our co-authors is certified as a supervisor of NEAR and she supervised NEAR sessions periodically. In order to use consistent methods across sites, all clinicians participated in 1-week clinician training, and they attended trimonthly meetings.

Although the medications were changed throughout the whole period as little as possible, there were 16 patients whose medications needed to be changed because of clinical decisions. However, the change in the medication status of these 16 patients was only related to daily dosage levels.

2.2. Assessments

We assessed cognitive function using the Japanese version of the Brief Assessment of Cognition in Schizophrenia (BACS-J) (Keefe et al., 2004; Kaneda et al., 2007). Z scores were calculated for each subcomponent score using means and standard deviations based on the dataset of 340 healthy control Japanese populations; however, it must be noted that age, sex, and socio-economic status of the healthy controls were not necessarily matched to those of the patients in the present study. Composite scores were calculated by averaging all z scores of the six subcomponents (verbal memory, working memory, motor speed, verbal fluency, attention and speed of information processing, and executive functions), and then re-normed based upon the standard deviations (SD) of the average of those scores in the normative sample (SD = 0.6).

2.3. Statistical analysis

Two-tailed paired t-tests were performed for the assessment of change between the two measurements of BACS-J data, which were administered before (baseline) and after (post-treatment) the NEAR sessions. Each subcomponent score was normally distributed except for the executive function score. Through a logarithmic transformation of the executive function score, the curve was modified to a normal distribution, described by [EX] = −log[2 − (Executive function BACS-J z score)]. Therefore, we used [EX] instead of "executive function BACS-J z score" for analysis.

Except for the treatment settings, baseline verbal memory, baseline [EX], and baseline composite scores, neither socio-demographic nor clinical variables differed significantly between the two groups (Table 1). Therefore, repeated measures analyses

Table 2
Sample educational computer software used in the computer sessions.

Task	Software	Activity	Target cognitive domain
The mail room	Monsters Inc.: Scream Team Training	Sort all the mail into the proper mailboxes before the clock hits 9 a.m.	Attention, speed
Lunch room	Monsters Inc.: Scream Team Training	Select food items and daily specials to serve to each monster in accordance with the figure presented on the lunch-order ticket.	Attention, speed
Moonfish	Finding Nemo: Nemo's Underwater World of Fun	Repeat the shape patterns made by the moonfish.	Working memory
Spark! Mejikara	Let's refresh your brain	Memorize the illustrations that appear one after another on the screen, and recollect them in order.	Working memory
Hustle memory	Let's refresh your brain	Memorize the character's clothes that are put on within 10 s.	Visual learning and memory
Frippletration	Thinkin' Things 2	Visual and auditory memory matching game.	Visual/auditory learning and memory
Stocktopus	Thinkin' Things 3	Repeat trading items to get the items you need for your portfolio.	Working memory, executive function,
Build it	Factory Deluxe	Build up the presented goal product by selecting and using appropriate tools.	Executive function
The puzzles	Logical Journey Of The Zoombinis	Solve puzzles with various rules using as clues physical features of hair, eyes, nose, and feet of little creatures called Zoombinis.	Executive function

"Thinkin' Things 2", "Thinkin' Things 3", and "Factory Deluxe" were English versions; however, English ability was not necessary to accomplish the tasks. Other software programs were Japanese versions.

Table 3
The result of paired *t* test on BACS-J data with NEAR participants.

	Baseline	Post treatment	*t*	*p*	Cohen's *d*
Verbal memory	−1.09 ± 0.92	−0.13 ± 0.99	8.80	<0.0001	1.01
Working memory	−0.95 ± 0.95	−0.54 ± 1.17	4.11	<0.0005	0.39
Motor speed	−1.60 ± 1.37	−1.04 ± 1.42	3.28	<0.005	0.41
Verbal fluency	−0.47 ± 1.00	−0.14 ± 1.10	3.41	<0.005	0.32
Attention and speed of information processing	−1.24 ± 0.88	−0.99 ± 0.96	3.19	<0.005	0.28
[EX]	−0.79 ± 0.59	−0.55 ± 0.55	3.02	<0.005	0.44
Composite score	−1.65 ± 1.27	−0.79 ± 1.33	8.96	<0.0001	0.67

[EX] = −log[2 − (Executive function BACS-J z score)].

of variance were performed on BACS-J data using 'group' (NEAR group, control group) and 'treatment settings' (inpatient, outpatient) as inter-individual factors, while 'time' (baseline, post-treatment) was used as an intra-individual factor. Moreover, in the analyses of verbal memory, [EX], and composite scores, baseline data were used as covariates.

3. Results (Tables 3, 4, Fig. 1)

3.1. The within-NEAR treatment change of BACS-J data

There were significant improvements in the scores of all subcomponents in the BACS-J (Table 3).

3.2. In comparison with control patients

There were significant interactions between 'group' and 'time' in verbal memory, working memory, verbal fluency, attention and speed of information processing, [EX], and composite scores (Table 4). The improvement of these areas was significantly greater in the NEAR group than in the control group. There was no difference between groups in terms of the change in motor speed.

4. Discussion

In the present study, we found significant improvement for all cognitive domains related to the BACS-J. According to the meta-analysis of the effectiveness of cognitive remediation in schizophrenia, neurocognitive benefit varied from small (Cohen's $d = 0.2$) to very large ($d = 1.2$) effect size (Medalia and Choi, 2009). Medalia et al. (2009) also suggested that heterogeneity of response to cognitive remediation might depend on instructional techniques, intellectual ability, and intrinsic motivation. In NEAR, instructional techniques are devised to enhance intrinsic motivation. It has already been shown that the use of NEAR educational software without an instructional approach did not achieve clinically meaningful change in neurocognitive capacity (Bellack et al., 2005; Dickinson et al., 2010). In our study, we complied with the principle of NEAR by attaching great importance to instructional approach and could find small to very large effect sizes in broad domains ($d = 0.28$–1.01). In comparison with the control group, the positive findings remained significant except for the motor speed. NEAR proved to be a feasible psychosocial therapy, even in Japan with its different cultural background and with the use of software programs that differ from those in Western countries.

In BACS-J, motor speed was assessed by the "Token Motor Task". The task requires the participants to put 100 plastic tokens into a container bimanually as quickly as possible within 60 s, and the outcome measure is the total number of tokens put in the container (Keefe et al., 2004). In the NEAR session, participants were engaged in the computerized learning tasks selected to address specific domains of cognitive function (Medalia et al., 2009); however, we may have failed to include those tasks that required considerable motor speed to perform in the session. This may explain why the NEAR participants were not able to achieve greater improvement in motor speed than the controls.

In this study, the two groups were heterogeneous in many points, and although several subcomponent scores of the BACS-J were significantly lower in the control group than in the NEAR group, correlations between baseline BACS-J data and the improvement in

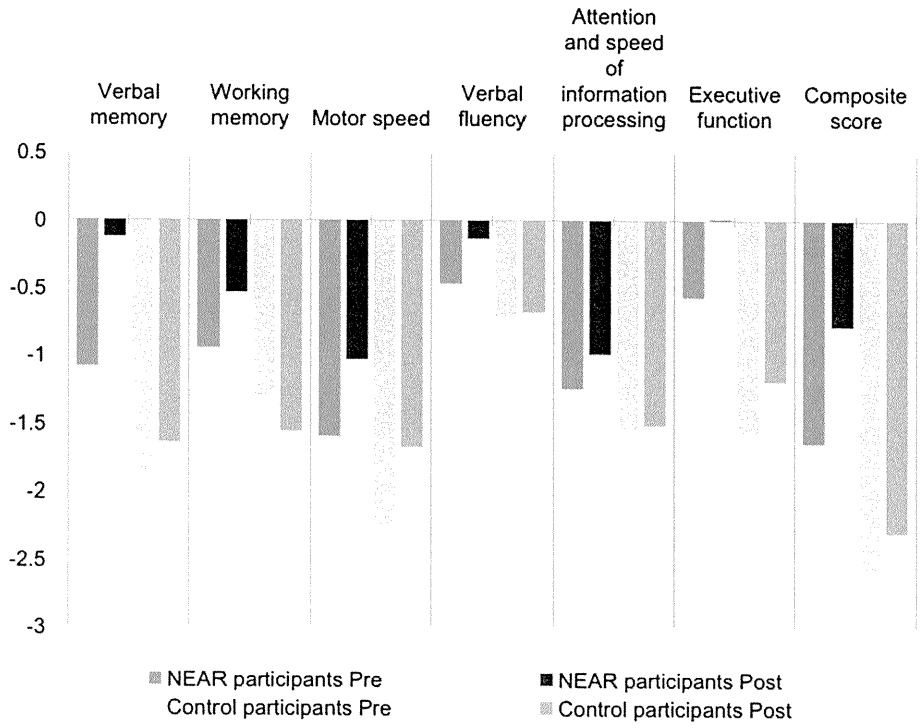

Fig. 1. Changes in cognitive function over a 6-month period.

Table 4
"Time × group" interaction effect on ANOVA with BACS-J data in comparison with control group.

	d.f.	F	p
Verbal memory#	1,69	16.1	<0.0005
Working memory	1,70	16.9	<0.0005
Motor speed	1,70	1.53	n.s.
Verbal fluency	1,70	4.39	<0.05
Attention and speed of information processing	1,70	5.79	<0.05
[EX]#	1,69	4.69	<0.05
Composite score#	1,69	19.1	<0.0001

# baseline data were used as covariates.
[EX] = −log[2 − (Executive function BACS-J z score)].

BACS-J data were negative ($r = -0.57$ to -0.06) in the NEAR group. This implies that the NEAR program is more effective when baseline neurocognitive ability is weaker. Although it is possible that there was recruitment bias to include higher functioning subjects in the NEAR group at baseline, it may be assumed that taking into account the difference in neurocognition would not negate the effect of NEAR.

There are several limitations of the present study. First, although only the difference in treatment settings between the NEAR participants and the controls appeared significant, clinical and demographic variables were not well matched between the two groups. Second, subjects were not randomly assigned to either of the groups. Third, some clinicians who managed the NEAR session also had to take a role as a tester in the BACS-J. To resolve these issues, randomized control studies of the NEAR program with testers being blinded to the treatment assignment are warranted. Moreover, while we focused on the neurocognitive effect of NEAR in Japan in the present report, we should also take into consideration its effectiveness on social function and/or quality of life in patients with schizophrenia.

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■統合失調症における薬物治療 ——❻

統合失調症における認知障害に対する非定型抗精神病薬の有効性

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Key Points

- 認知障害は統合失調症の病態の中核であり，長期予後や機能的転帰などの臨床特徴を決定する．
- 非定型抗精神病薬は認知障害を軽度改善するが，その効果は慢性統合失調症では定型抗精神病薬より明らかに優れているとは言い難い．
- 非定型抗精神病薬は精神病の初発患者や超ハイリスク者の一部で明らかに認知機能を改善し，その場合，長期予後を改善することが期待される．
- 米国においては，産学官民連携で認知機能自体を治療標的とした創薬が展開している．

はじめに

認知障害は，統合失調症が疾患として提唱された約1世紀前からすでに，その病態の中核と考えられてきた．統合失調症でみられる認知障害は認知機能全般にわたる障害であるが，とくに注意，記憶，実行機能の障害が目立ち，精神病症状の発症以前から出現することが明らかになってきた[1)]．なお，その障害の質と経過の特徴は，認知症でみられる認知障害とはまったく異なる．また，統合失調症でみられる認知障害は，治療の最終目標となる長期予後や機能的転帰に対して精神症状以上に強い影響力をもっていることが明らかになり，最近では認知障害を統合失調症の診断基準に加えようとする動きや[2)]，認知障害自体を統合失調症の治療標的と位置づけた新たな認知改善薬の開発がかなり進展している[3)]．

なぜ認知障害か？

図1はAndreasen[4)]によって提唱された統合失調症の病態である．病因には遺伝因と環境因が想定され，いわゆる多因子病と考えられ，一方の要因だけでは発症せず両者の相互作用で発症すると推定されている．遺伝因には数十個の候補遺伝子(遺伝子多型など)が見つかっており，一方，環境因には胎生期も含めて発症前までのさまざまな脳器質性損傷と心理社会的要因が知られている．こうした複合的病因によってニューロンの発達が障害され，脳の構造的変化や機能的変化が起こり，最終的に神経伝達物質の偏倚を伴う神経ネットワークの機能障害に帰結する．これを基盤にして，基本障害としての認知障害が出現し，何らかの引き金によって精神症状や行動変化がもたらされると考えられている．

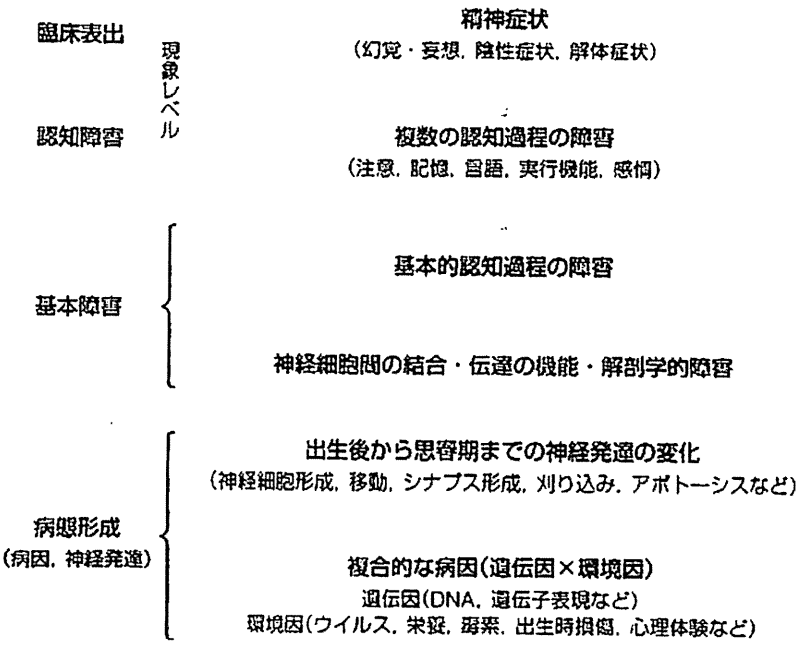

図1 統合失調症の病態モデル

(文献4)より引用改変)

したがって，図1のように認知障害は病態の中核に位置し，病因研究における生物学的指標となる．一方で，認知障害は精神症状の基盤にあることから，診断的に重要な意味をもち，本質的な治療標的になることが理解できよう[5]．なお，従来の第1世代(定型)抗精神病薬のドパミン遮断による抗幻覚妄想作用は，精神症状次元に対する対症療法の意味合いが強い．

非定型抗精神病薬への期待と現実

1 抗精神病薬開発の歴史

1950年代にフェノチアジン系のクロルプロマジンが登場し，統合失調症の本格的な薬物療法が始まり，第1世代の"定型"抗精神病薬によって幻覚，妄想を中心とした陽性症状に対する治療が進展し，これとともに統合失調症のドパミン(D_2)仮説が確立されていった．

しかし，陽性症状以外の意欲・感情面や対人機能面の障害である陰性症状の治療が立ち遅れ，ドパミン(D_2)以外の神経伝達物質への関心が高まるとともに，一方で社会技能訓練をはじめとした心理社会療法が発展した．

1990年代には定型抗精神病薬による錐体外路性副作用の出現しにくいserotonin dopamine antagonist (SDA)やmulti-acting receptor targeted agent (MARTA)と呼ばれる第2世代の"非定型"抗精神病薬が続々と登場し，陰性症状やさらに認知障害に対する治療効果が期待されるようになった．

2 非定型抗精神病薬の認知改善作用への期待

非定型抗精神病薬は，定型抗精神病薬の特徴であるラットでのカタレプシー惹起作用(黒質・線条体のドパミン遮断による)が弱いかほとんどないため"非定型"と呼ばれるが，最大の利点は副作用としての錐体外路症状(パーキンソニズムなど)の回避である．

認知機能に対する影響に関しては，定型抗精神病薬では，①ドパミン(D_2)遮断作用による実行機能や反応速度の障害，②フェノチアジン系抗精神病薬および錐体外路性副作用に対して投与する抗パーキンソン病薬による学習・記憶の障害などにより認知機能を悪化させる可能性がある．一方で，非定型抗精神病薬では，①ドパミン遮断作用が弱いために実行機能や反応速度の障害が起きにくく，②内在性抗コリン作用が弱いために抗パーキンソン病薬の投与が不要な場合が多く，さらに③セロトニン$5HT_{2A}$拮抗作用による前頭葉でのドパミン増加に伴う実行機能の改善や[6]，グルタミン酸系NMDA受容体への作用による積極的な認知機能の改善が期待された．

3 認知改善作用に関する定型および非定型抗精神病薬の比較研究

1993～2004年までに公表された定型と非定型の抗精神病薬を比較した初期の41研究のメタ解析では[7]，定型抗精神病薬と比較して非定型抗精神病薬は，学習，処理速度，言語流暢性，運動技能の改善に関して軽度ではあるが優れていた．また，非定型抗精神病薬の間では注意や言語流暢性などにおいて認知改善のプロフィールが異なることも示された．しかし，研究方法上のさまざまな問題(練習効果，スポンサーシップ，公表バイアス，前治療薬や抗コリン薬の影響など)も指摘され，明確な結論は得られなかった．

非定型抗精神病薬の優位性を示すために，定型抗精神病薬としてしばしばブチロフェノン系のハロペリドールが比較に用いられる．しかし，上述のようにもし定型抗精神病薬が認知機能を悪化させるとしたら，それとの比較でみた非定型抗精神病薬の認知改善は見かけ上のものかもしれない．ハロペリドールの認知機能への影響を検討した研究のメタ解析では[9]，ハロペリドールによって処理速度と言語流暢性は悪化するが認知機能全体としてはわずかに改善することから，ハロペリドールとの比較で報告されてきた非定型抗精神病薬の認知改善は，処理速度と言語流暢性を除き真の効果である可能性が示唆された．

最近，米国の多施設による大規模研究で有名なCATIE研究(The Clinical Antipsychotic Trials of Intervention Effectiveness study)において，定型(ペルフェナジン)と非定型(オランザピン，リスペリドン，クエチアピン，わが国では未発売のziprasidone)の抗精神病薬の認知改善作用が817人の統合失調症患者で比較された[8]．治療18ヵ月後の時点で，すべての薬剤で軽度の認知改善作用を認めたが，予想に反してフェノチアジン系のペルフェナジンによる効果がもっとも優れており，しかもそれはオランザピン，リスペリドンより有意に優れていた．健常者84人を対照群として，初発の統合失調症患者104人におけるオランザピンとリスペリドンの認知改善効果を検討した研究で[10]，これらの薬剤で改善した認知機能の程度は，健常者における検査反復に伴う一種の学習効果(練習効果：practice effect)とほぼ同等であり，薬物自体による純粋の認知改善は乏しいことが指摘された．

以上のように，認知機能に対する非定型抗精神病薬の改善作用はわずかなものであり，統合失調症の長期予後や機能的転帰を確実に改善するものとは考えがたく，非定型抗精神病薬の認知改善に関する有用性は誇張されすぎてきたといえる[11]．たとえば，統合失調症では，記憶，注意，作業記憶，問題解決，処理速度，社会認知で，健常者の平均値と比べて標準偏差(SD)の1.5～2倍以下の遂行障害を示すが[2]，非定型抗精神病薬での認知改善の程度は練習効果を含めてSD×0.2～0.4であり[7]，統合失調症でみられる認知障害を十分

に改善し，病前の機能状態まで回復させることは期待できない．なお，認知障害以外の陽性症状，陰性症状，気分症状に関しては，重篤な副作用(無顆粒球症など)を惹起しやすいクロザピンだけが薬物治療抵抗性患者において明らかに有効であるが，ほかの非定型ならびに定型抗精神病薬のなかで突出した効果を示す薬剤はなく，現時点では抗精神病薬は個人ごとに有用性と安全性のバランスで経験的に選択せざるを得ない[11]．

4 非定型抗精神病薬の認知改善作用に関する今後の課題

前述のCATIE研究では，対象患者の平均年齢は40.9歳で，平均治療期間は14.3年と慢性患者が大半を占めていた[8]．ところで，前駆期から発症後の早期経過(3～5年程度)における治療が，長期予後に大きく影響するという臨界期仮説がある．この仮説は，脆弱ではあるが可塑性のある臨界期に十分な治療を行うことで，精神病の予後や経過が改善されることを含意している[1]．この視点から，初発患者や近年研究が急速に進展してきた精神病の超ハイリスク者に対する早期介入において，非定型抗精神病薬による認知改善作用が期待されているが研究はまだ少ない．

精神病の初回エピソードに関する最近の研究で[12]，入院した77人の未治療患者を対象に，無作為にリスペリドンとオランザピンを割り付け，ベースライン(入院当日で，薬物未投与)，1ヵ月後，6ヵ月後と認知機能を評価した．治療後6ヵ月時点で対象患者の30%において，ベースラインから17～54%の認知改善を示した．さらに，途中で薬物が中止となった群も6ヵ月時点で治療継続群と同等の認知改善を示したことから，薬物による認知改善作用は投与後数ヵ月以内で出現し，それが薬物継続の有無とは関係なく少なくとも6ヵ月時点まで持続することが示された．この結果は，非定型抗精神病薬で認知が改善する"著効例"の存在を示唆しており，多くの臨床家が実感しているところでもある．この研究での著効例の予測因子としては，ベースラインでの認知障害の程度が強いこと，次に病前の低い学業成績やIQなどが特定された．

萌芽的な精神病症状が出現している超ハイリスク者を対象として，薬物療法と心理社会療法を組み合わせた包括的治療によって認知機能が改善するかどうかを検討した研究で[13]，対象患者の半数で20%以上の社会機能と役割機能が改善し，それらは認知機能(学習・記憶，処理速度，運動速度)の改善と関連していた．したがって，超ハイリスク者の一部において，早期の包括的治療介入が長期予後や機能的転帰を改善させる可能性がある．ただし，この研究では非定型抗精神病薬が使用されたのは対象の約半数においてであり，ほかは抗うつ薬や感情調整薬が投与されており，認知改善が非定型抗精神病薬によるものかどうかは明らかになっていない．

認知改善薬の開発に向けてのパラダイムシフト

米国では産学官民の連携で，新たな認知改善(認知増強)薬の開発が進んでいる．具体的には，病態の中核的な認知障害を明らかにして，創薬の標的となる認知評価バッテリーと研究デザインの確立を目指したMATRICSプロジェクト(Measurement and Treatment Research to Improve Cognition in Schizophrenia project)と，認知改善薬の選択と有用性の評価のための研究ネットワークであるTURNSプロジェクト(Treatment Units for Research on Neurocognition and Schizophrenia project)を立ち上げて創薬が展開し

表3 認知改善薬の候補

	認知障害改善作用	精神症状改善作用
コリン作動薬		
DMXB-A（α_7-ニコチン作動薬）	＋	－
xanomeline（ムスカリンM_1, M_4作動薬）*	＋	＋（症状全般）
ドネペジル（Ach分解酵素阻害薬）	－	－
rivastigmine（Ach分解酵素阻害薬）	－	－
galantamine（Ach分解酵素阻害薬）	＋	－
ドパミン作動薬		
DAR-0100（dihydrexidine）（D_1作動薬）	－	－
グルタミン酸作動薬		
glycine（NMDA受容体作動薬）	－	＋（陰性症状）
D-cycloserine（NMDA受容体作動薬）	－	＋（陰性症状）
D-alanine（NMDA受容体作動薬）	－	＋（陰性症状）
sarcosine（NMDA受容体作動薬）	－	△（症状全般）
GLYT1 inhibitors（NMDA受容体作動薬）	－	－
AMPAkines（CX-516）（AMPA受容体作動薬）	＋	－
mGlu2/3作動薬（代謝調整型受容体作動薬）	未検	＋（陽性症状）

＊：文献14）より追加.
＋：効果あり　－：効果なし　△：やや効果あり

（文献3）より引用改変）

ている[3]．現在，認知改善薬の候補にあがっているのは以下の通りである．

1）アセチルコリン作動薬：抗認知症薬の治療標的でもある．注意，記憶，処理速度，感覚ゲーティングの改善が期待される
2）ドパミン作動薬：ドパミン（D_1）と関連し中脳皮質系回路などを介した前頭葉の作業記憶，実行機能の改善が期待される
3）グルタミン酸作動薬：NMDA受容体の拮抗薬（PCP，ケタミン）は中毒精神病を惹起するが，作動薬は神経発達，神経可塑性と関連して認知機能の改善が期待される．

具体的な開発状況を表1に示した[3, 14]．

おわりに

統合失調症は，均一な原因，病態，症状，経過，治療反応性を示す単一疾患ではなく，病態の"異種性"が指摘されている[15]．これは，個々の抗精神病薬による認知改善作用に著効例と無効例があることからも肯けよう．したがって，近い将来には個々の患者の特徴にあわせた個別化された治療が求められるようになるが，その際に臨床症状以上に認知障害の特徴が重要になるであろう．

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Psychosis早期段階における心理学的要因

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