It has been proposed that schizophrenia is a neurodevelopmental disorder caused by insults in the second trimester (Roberts 1991), which results in an abnormal development of the frontal cortex. This developmental change becomes clinically overt at the time of sexual maturation, and is associated with subsequent dysregulation of the neural system (Weinberger 1995). Morphological studies have demonstrated a reduction in the volume of the prefrontal cortex and the temporal lobes in schizophrenia (Kawasaki et al. 2004; Suzuki et al. 2005). These findings lead to the hypothesis that latent dysfunction of the temporal regions becomes overt by additional pathological changes in the frontal lobes, leading to manifestation of positive psychotic symptoms (Kurachi 2003a, b; Siever and Davis 2004). This hypothesis is supported by animal studies which found inactivation of the medial prefrontal cortex (mPFC), in subjects with structural abnormalities in the entorhinal cortex leads to dysregulation of dopaminergic neurotransmissions in the limbic regions, such as the amygdala and nucleus accumbens (Uehara et al. 2000, 2003, 2004, 2007).

Several researchers have attempted to develop animal models of schizophrenia using rats based on the neurodevelopmental hypothesis or the NMDA-receptor-dysfunction hypothesis (Beninger et al. 2002; Harris et al. 2003; Rasmussen et al. 2007; Stefani and Moghaddam 2005; Takahashi et al. 2006; Wang et al. 2001). Treatment of neonatal rats with non-competitive NMDA antagonists (e.g., MK-801, phencyclidine) led to behavioral abnormalities related to clinical symptoms of schizophrenia (e.g., locomotor activity, prepulse inhibition; Prepulse inhibition (PPI), spatial memory test) in the adult stage. Moreover, Stefani et al. reported that neonatal treatment with MK-801 (0.20 mg/kg/day) between postnatal day (PD) 7 and 10 led to frontal dysfunction in adult rats, such as impairment of the set-sifting test (Stefani et al. 2003; Stefani and Moghaddam 2005).

A sudden strong acoustic stimulus produces acoustic startle response in both humans and rodents. PPI is a phenomenon defined as reduction in startle reflex by prior presentation of a weak, non-startling stimulus (Graham 1975; Hoffman and Searle 1968), and has been used as a measure of sensorimotor gating. PPI can be measured both in human and animals, and is disrupted in patients with schizophrenia (Braff et al. 1992, 1999). NMDA antagonists have been shown to produce PPI deficits in animals (Bubenikova et al. 2005; Seo et al. 2008). However, conflicting results exist about long-term effects of postnatal NMDA receptor blockade on PPI. Some studies demonstrated that postnatal exposure to NMDA antagonists disrupts PPI in adult stage (Takahashi et al. 2006; Wang et al. 2001), whereas others did not find such an effect (Harris et al. 2003; Rasmussen et al. 2007).

The aim of this study was to determine whether a brief disruption of NMDA receptor function by MK-801 during the neonatal stage would produce sensorimotor-gating deficits in the late adolescence or early adulthood. For this purpose, we administered MK-801 to rats on PD 7–10 (Stefani and Moghaddam 2005), because this animal model has been shown to elicit frontal dysfunction at these later stages, an important component of the pathophysiology of schizophrenia (Kurachi 2003a, b; Siever and Davis 2004; Weinberger 1995).

Materials and methods

Animals

Female Wistar rats obtained at 14 days of pregnancy (Japan SLC, Japan) were housed individually at 24±2°C under a 12-h light (0700–1900 h)–12-dark cycle with free access to food and water. At the time of weaning (PD 25), the animals were grouped into four to six in each same treatment, described in the next paragraph, in a cage with free access to food and water. The procedures complied with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. All experiments were reviewed and approved by the Committee of Animal Research, University of Toyama School of Medicine.

Treatments

On PD 7, male pups (10–15 g) were randomly assigned into three groups. They received MK-801 (Sigma-Aldrich, St. Louis, MO, 0.13 or 0.20 mg/kg s.c.) or equal volume of saline (vehicle group). From PD 7 to PD 10, pups were injected with drugs, between 8:00–10:00. All pups from the same litter received the same treatment (low-dose MK-801; two litters, high-dose MK-801; two litters, vehicle; two litters) to avoid the influence of cross-fostering and minimize maternal care effects. There were no statistical litter effects on all parameters in this study.

Apparatus and procedure of PPI

Rats in each group were tested twice for PPI on PD 35 and PD 56. The procedure of PPI measurement was based on our previous studies (Seo et al. 2008; Uehara et al. 2007). All testing occurred within startle chambers (Ohara & Co., LTD, Tokyo), which was housed in a sound-attenuated room with a 60 dB ambient noise level. Each startle chamber consisted of a Plexiglas cylinder 9.4 cm in internal diameter resting on an 11 cm×22 cm Plexiglas stand. Acoustic stimuli and background noise were given via speakers mounted 12.2 cm above the Plexiglas cylinders,

controlled with a computer box (Ohara & Co., LTD, Tokyo). A piezoelectric device mounted below the Plexiglas stand detected and transduced motion within the cylinder.

Rats were placed in a startle chamber. Five minutes after the acclimation period, they were exposed to six blocks of four different stimulus types, i.e., pulse-alone: 40 ms 120 dB white noise bursts; prepulse-pulse: 20 ms, white noise pulse of 70, 74, 78, 82 and 86 dB followed by 20 ms 120 dB white noise pulse at a fixed inter-stimulus interval (ISI) of 100 ms. Trials were presented in randomized order, with 20, 25, and 30 s randomized interval.

Locomotor activity

After the PPI examination, spontaneous activity was measured for 30 min in an ambulation observation chamber (blackened vinyl chloride cages, 40 cm× 40 cm×40 cm; AMB-3001, Ohara & Co., Ltd., Tokyo, Japan) equipped with 6×6 photoelectric light sources spaced at 7-cm intervals and 2.5 cm (for locomotor activity) above the floor (AMB-2020, Ohara & Co., Ltd.; Sumiyoshi et al. 2004; Uehara et al. 2007). Rearing was measured photoelectric light sources spaced at 12 cm (on PD 36–38) or 19 cm (on PD 57–59) above the floor. Interruptions of light beams were registered as activity counts, and were summarized every 5 min by the Logger Interface control system (IF-10-LOG, Ohara & Co., Ltd.). For convenience, the test days are referred to as PD 35 and PD 56 throughout the manuscript.

Presentation of the results and statistics

Data were analyzed by analysis of variance (ANOVA) using SPSS software (version 16.0 J for Mac, SPSS Inc.). For comparison of body weight, two-way repeated measures ANOVA was performed with treatment status (Status= low-dose MK-801, high-dose MK-801, vehicle) as between-subject factor and age (PD 35 and PD 56) as repeated measures variable, followed by Tukey's HSD test.

PPI data were presented as percentage of PPI (%PPI), which was calculated from startle amplitudes (SAs) using the following formula: %PPI=100−[(SA for prepulse-pulse trials)/(SA for pulse-alone trials)]×100. Between-group comparisons were performed by three-way repeated measures ANOVA with treatment status (Status=low-dose MK-801, high-dose MK-801, vehicle) as between-subject factor, whereas prepulse intensity and age (PD 35 and PD 56) were treated as repeated measures variables. If treatment×age interaction was significant, two-way repeated measures ANOVA were performed with treatment status as between subject and prepulse intensity as repeated measures variables at each age (PD 35 and PD 56) separately. For comparisons of SAs, two-way repeated measures ANOVA was performed with treatment status as between-subject factor and age was treated as repeated measures variable. Post-hoc comparisons were made between all treatment groups with Tukey's HSD test.

For comparisons of locomotor activity, we divided the time for activity counts into two time-intervals (0–15 min and 16–30 min). Three-way repeated measures ANOVA was performed with treatment status as between-subject factor, whereas age (PD 35 and PD 56) and time (first-half interval and second-half interval) as repeated measures variable followed by Tukey's HSD test. A probability (P) of less than 0.05 was considered to be significant.

Results

Effect of neonatal MK-801 treatment on body weight across development

ANOVA revealed a significant main effect of treatment [$F(2,32)=145.0$, $P<0.0001$] and treatment×age interaction [$F(2,32)=30.9$, $P<0.0001$]. Tukey's HDS test demonstrated a significant reduction of body weight in low MK-801 group compared to controls ($P=0.005$), and that body weight of high-dose MK-801 group was smaller than that of low-dose MK-801 group ($P<0.0001$) and controls ($P<$ 0.0001; Table 1).

Effect of neonatal MK-801 treatment on startle and prepulse inhibition

Two-way repeated measures ANOVA demonstrated a significant treatment×age interaction effect on SAs [$F(2,32)=5.13$, $P=0.012$]. Because there was a significant treatment×age interaction effect, subsequent analysis was conducted to examine the main effect of the treatment status on PD 35 and PD 56 separately. There was no significant main effect of the treatment status on PD 35, whereas a significant effect was found on PD 56 [$F(2,32)=$ 10.01, $P<0.0001$]. Tukey's HSD test revealed that low-dose MK-801 increased SAs compared to vehicle ($P<$

Table 1 Body weight across development

Treatment groups	Postnatal day	
	PD 35	PD 56
Vehicle ($n=10$)	126.2±1.5	295.2±3.7
MK-801 (0.13 mg/kg) ($n=12$)	114.2±1.6	282.8±3.5
MK-801 (0.20 mg/kg) ($n=13$)	86.8±2.0	224.6±4.3

0.0001), and high-dose MK-801 (P=0.036). No significant difference was found between vehicle and high MK-801 groups (P=0.12; Fig. 1).

Three-way ANOVA revealed a significant treatment×age interaction [$F(2,32)$=3.89, P=0.031] and main effect of treatment [$F(2,32)$=7.20, P=0.003] on PPI (Fig. 2). There was no significant treatment×prepulse intensity interaction effect [$F(8,128)$=1.22, P=0.29]. These results revealed that neonatal MK-801 treatment affected the changes of PPI with development around puberty.

Subsequent analysis was conducted to examine main effect of treatment on PD 35 and PD 56 separately. On PD 35, a significant main effect of treatment status [$F(2,32)$=3.60, P=0.04], but not treatment status×prepulse intensity interaction [$F(2,32)$=2.13, P=0.14] on PPI was noted. Tukey's HSD test revealed that low-dose MK-801 reduced PPI compared to vehicle treatment (P=0.03). However, there was no significant difference in PPI between vehicle and high MK-801 groups (P=0.49). On PD 56, a significant main effect of treatment status [$F(2,32)$=7.45, P=0.002] and treatment status×prepulse intensity interaction [$F(2,32)$=3.47, P=0.04] on PPI was found. Tukey's HSD test demonstrated a significant reduction of PPI in high-dose MK-801 group compared to vehicle group (P=0.001). There was no difference in PPI between vehicle and low MK-801 groups (P=0.15) on PD 56 (Fig. 2).

Effect of neonatal MK-801 treatment on locomotor activity

There was no significant treatment × age interaction [$F(2,32)$=1.97, P=0.16], or treatment × time interaction [$F(2,32)$=0.57, P=0.57] on locomotor activity. Moreover, no significant main effect of treatment status [$F(2,32)$=2.46, P=0.10] was found (Fig. 3). On the other hand, significant treatment×time interaction [$F(2,32)$=8.71, P=0.001] and main effect of treatment status [$F(2,32)$=12.7, P<0.0001] on rearing were noted. However, there was no significant treatment×age interaction [$F(2,32)$=2.03, P=0.15]. Tukey's HSD test revealed no significant difference in rearing between vehicle vs. low-dose MK-801 groups (P=0.102), whereas high-dose MK-801 treatment produced a decrease in rearing compared to vehicle (P=0.034) and low-dose MK-801 (P<0.0001) groups (Fig. 4).

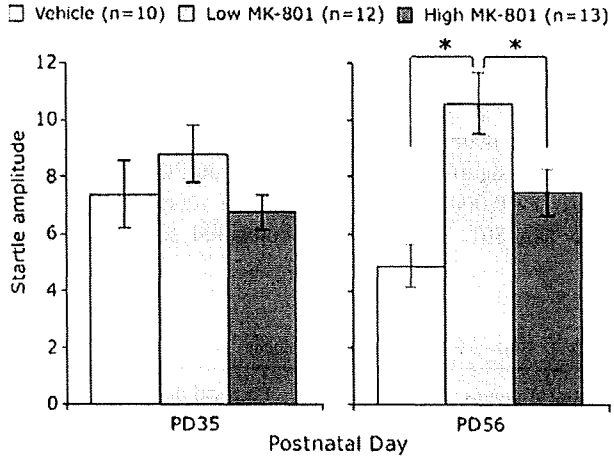

Fig. 1 Mean startle amplitudes on single noise (120 dB) trials during prepulse inhibition (PPI) sessions. Data of vehicle group, low-dose MK-801 group, high MK-801 group are shown by *open bars*, *shaded bars*, and *dark bars*, respectively. Values are expressed as mean± SEM. *Asterisks* denote significant group differences (P<0.05)

Discussion

The present study demonstrates that transient, neonatal exposure to MK-801 induces disruption of sensorimotor gating in the adolescence and early adulthood. Low-dose MK-801 (0.13 mg/kg) elicited long-term effects on SAs, whereas a higher dose (0.2 mg/kg) did not on PD35 and 56. Treatment with low-dose MK-801 led to reduction of PPI without any effect on SAs on PD 35. PPI on PD 56 was not affected by low-dose MK-801, whereas SAs were increased. By contrast, high-dose MK-801 disrupted PPI only on PD 56 without any effect on SAs. On the other hand, either dose MK-801 did not affect spontaneous locomotor activity, although only the high dose decreased rearing activity.

Neonatal MK-801 treatment inhibited weight gain across development, replicating the results of a previous study (Stefani and Moghaddam 2005). Results in this study further revealed the effect of MK-801 on body weight is dose-dependent. In this study, all pups from the same litter received the same treatment to avoid the influence of cross-fostering and minimize maternal care effects. There were no statistical litter effects on all parameters (data not shown). In fact, only two litters were used in each treatment group, which may not be enough to detect any litter effects.

In this study, both doses of MK-801 disrupted PPI in pre- (PD 35) and post- (PD 56) puberty. Conflicting results have been reported on long-term effects of postnatal NMDA receptor blockade on PPI. Treatment with PCP (10 mg/kg, s.c.) on PD 7, 9, and 11 disrupted PPI on PD 24-26 (Wang et al. 2001), but not on PD 32, 39, 51, 72, and 88 (Rasmussen et al. 2007). In the former study, olanzapine reversed PCP-induced PPI disruption (Wang et al. 2001). MK-801 treatment (0.5 or 1.0 mg/kg, i.p.) on PD 3 did not affect PPI on PD 35 and 56, whereas it reduced sensitivity to prepulse intensity changes on PD 56 (post-puberty), but not on PD 35 (Beninger et al. 2002). On the other hand, MK-801 (0.5 mg/kg, s.c.) treatment on PD 7 did not affect PPI on PD 56 (Harris et al. 2003). These results suggest

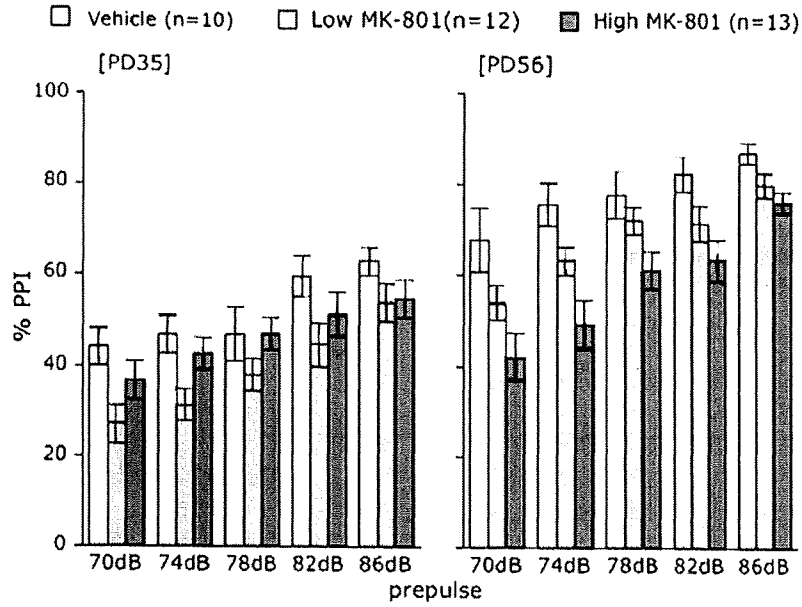

Fig. 2 Effect of neonatal MK-801 treatment on PPI tested on PD 35 and PD 56. Data of vehicle group, low-dose MK-801 group, and high-dose MK-801 group are shown by *open bars*, *shaded bars*, and *dark bars*, respectively. Values are expressed as mean±SEM

that postnatal treatment with NMDA antagonists diminishes sensorimotor gating transiently around the time of puberty (Rasmussen et al. 2007).

Results of the current study revealed that administration of MK-801 on PD 7–10 elicits prolonged effect on disrupted PPI. Treatment with PCP (2 or 10 mg/kg, s.c.) from PD 3 to PD 16 has been shown to diminish PPI in 8-week-old rats (Takahashi et al. 2006). Overall, the ability of NMDA receptor blockade during the neonatal period to disrupt PPI may depends on treatment duration. It is also worthwhile to note that studies using Sprague–Dawley (SD) rats did not demonstrate PPI disruption induced by postnatal treatment of NMDA antagonists, unlike the results of current study using Wistar rats. This may represent stain-dependent effects of PCP on PPI, as has been reported in an acute study (Varty and Higgins 1994).

MK-801 treatment (0.20 mg/kg/day) between PD 7 and PD 10 has been shown to impair performance on the set-shifting test (Stefani et al. 2003; Stefani and Moghaddam 2005), a measure of medial prefrontal cortex (mPFC) function which is dependent on NMDA receptor-mediated neurotransmission (Stefani and Moghaddam 2003). These previous results indicate that MK-801 treatment in the neonatal period impairs NMDA receptor function in the mPFC in matured rats. On the other hand, PPI is thought to be regulated by the prefrontocortico-

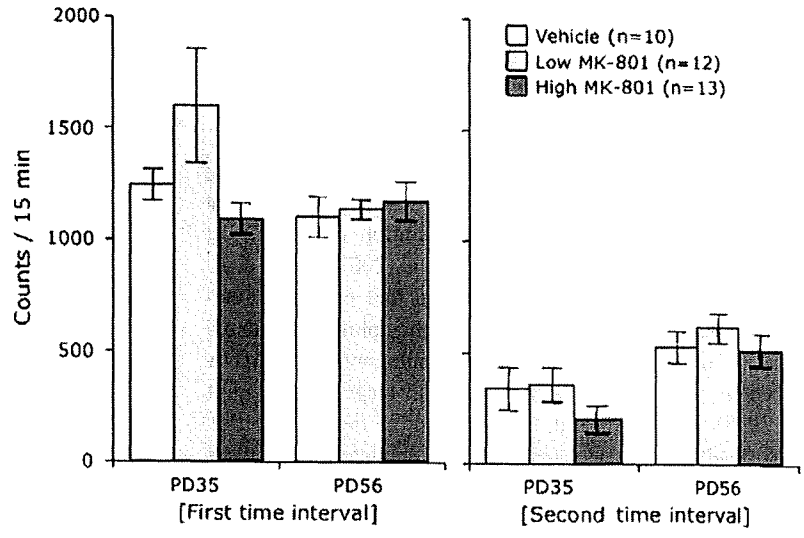

Fig. 3 Effect of neonatal MK-801 treatment on locomotor activity during the first time interval (0–15 min) and second time interval (16–30 min). Data of vehicle group, low-dose MK-801 group, and high-dose MK-801 group are shown by *open bars*, *shaded bars*, and *dark bars*, respectively. Values are expressed as mean±SEM

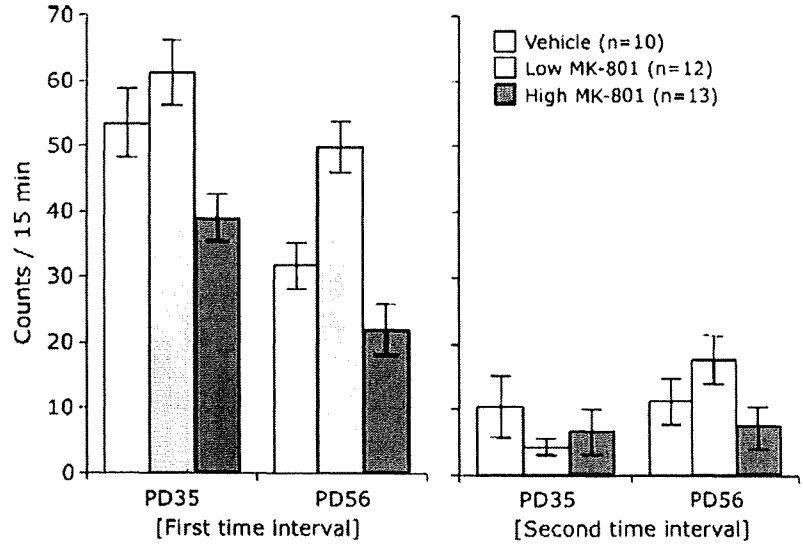

Fig. 4 Effect of neonatal MK-801 treatment on rearing during the first time interval (0–15 min) and second time interval (16–30 min). Data of vehicle group, low-dose MK-801 group, and high-dose MK-801 group are shown by *open bars*, *shaded bars*, and *dark bars*, respectively. Values are expressed as mean±SEM

limbic-striato-pallidal circuit that connects to the primary acoustic startle response pathway through mesopontine and nigral projections (Swerdlow et al. 2001). NMDA receptors in the mPFC, amygdala, and hippocampus play an important role in this circuit (Bakshi and Geyer 1998; Schwabe and Koch 2004). These lines of evidence suggest the role of NMDA receptor blockade by neonatal exposure to MK-801 in the manifestation of PPI disruption in a later period, as observed in this study.

Prenatal administration (E15-E18) of MK-801 has been reported to decrease the number of parvalbumin-positive GABAergic interneurons in the mPFC in adult rats (PD 35 and 63; Abekawa et al. 2007). Manipulations to decrease GABAergic transmissions in the mPFC have been shown to disrupt PPI, presumably by disinhibition of descending glutamatergic fibers (Japha and Koch 1999; Schwabe and Koch 2004; Swerdlow et al. 2001). Further studies are warranted to determine if histochemical changes of parvalbumin-positive GABAergic interneurons are present in the animal model studied here.

Low-dose MK-801 enhanced SAs on PD 56, whereas high-dose MK-801 did not affect them. This finding appears not consistent with previous studies reporting that neonatal NMDA antagonist administration did not affect SAs in the later stage (Rasmussen et al. 2007; Wang et al. 2001). However, it was also reported that postnatal treatment with (*E*)-2-amino-4-methyl-5-phostphno-3-pentenoic acid (CGP 40116), a competitive antagonist at NMDA receptors, increased SAs in early adult stage (Wedzony et al. 2008). The increase in the amplitude of the startle reflex may result from supersensitivity of glutamatergic receptors in the ventral nucleus of the lateral lemniscus (VLL) and the caudal pontine reticular nucleus (PnC; Krase et al. 1993; Spiera and Davis 1988). Moreover, repeated (PD 7,9,11), but not single (PD 7), injection of PCP reduces the number of the NMDA receptors in the striatum, whereas both sub-chronic and single injection of PCP increases the number of these receptors in the frontal cortex (Anastasio and Johnson 2008). These results suggest that functional changes of NMDA receptors induced by neonatal treatment with NMDA antagonists depends on dose and region.

Neonatal exposure to MK-801 did not affect locomotor activity. This finding is in line with previous studies reporting that neonatal treatment with NMDA receptor antagonists did not affect novelty-induced and spontaneous locomotor activity both in pre- and post-pubertal periods (Beninger et al. 2002; Harris et al. 2003; Stefani and Moghaddam 2005). Rats treated with NMDA receptor antagonists in the neonatal period showed enhanced PCP (Wang et al. 2001) or amphetamine-induced (Beninger et al. 2002) locomotor activity. On the other hand, we found enhancement of rearing on PD 56 in rats treated with low-dose MK-801. MK-801 treatment (0.5 and 1.0 mg/kg) on PD 3 has been shown to enhance amphetamine-induced rearing activity at PD 35 and PD 56 (Beninger et al. 2002). These findings suggest that NMDA receptor blockade at a neonatal period caused behavioral changes related to dopamine supersensitivity around puberty.

In conclusion, neonatal exposure to MK-801 disrupted PPI in the adolescence and early adulthood, possibly associated with NMDA receptor dysfunction in the mPFC. In view of the neurodevelopmental and NMDA hypotheses of schizophrenia, these findings indicate that rats transiently exposed to NMDA blockers in neonatal periods are useful for the study of the pathophysiology and treatment of schizophrenia.

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THOUGHT DISORDER AND EXECUTIVE DYSFUNCTION IN PATIENTS WITH SCHIZOPHRENIA

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Although, impairment of executive functioning is often reported in schizophrenia, its association with thought disorder has not been fully determined. The present study examined the relationships between positive thought disorder assessed using the Harrow's Thought Disorder Scale (Harrow's scale) and executive function by Wisconsin Card Sorting Test (WCST) in 27 inpatients with schizophrenia. Age at onset exhibited a significant negative correlation with Wechsler Adult Intelligence Scale comprehension test score of Harrow's scale and a significant positive correlation with percentage of perseverative errors on the WCST. No significant correlations were found between parameters of positive thought disorder and executive function. Thought disorder and executive function may play different roles in the pathophysiology of schizophrenia.

Keywords executive function, Harrow's Thought Disorder Scale, perseverative error, schizophrenia, thought disorder, Wisconsin Card Sorting Test (WCST)

INTRODUCTION

Although, thought disorder is present to some extent in all types of psychoses, it appears to be a key symptom in patients with schizophrenia. Positive thought disorder is one of the several central features of active schizophrenia, and is reported to remain either persistently or episodically present. Positive thought disorder is related to concurrent functioning, and predicts poorer outcome and function in patients with schizophrenia (Harrow & Marengo, 1986; Harrow, Marengo, & McDonald, 1986; Marengo & Harrow, 1987; Racenstein, Penn, Harrow, & Schleser, 1999). Harrow et al. reported that severity of thought disorder was stable over time and correlated with level of adjustment at follow-up (Harrow & Marengo, 1997). However, another study found no significant correlation between thought disorder and clinical variables in schizophrenia (Kazumdar, Chaturvedi, & Gopinath, 1994).

Harrow's Thought Disorder Scale (Harrow's scale) is one means of assessment of the type and severity of thought disorder (Harrow & Quinlan, 1985). This scale is also called the Comprehensive Index of Positive Thought Disorder (CIPTD) (Marengo, Harrow, Lanin-Kettering, & Wilson, 1986). It is used to evaluate patients for the presence and severity of thought disorder. The scores have been found to correlate significantly with those of Johnston and Holzman's Thought Disorder Index (Marengo et al., 1986). Harrow's

scale consists of the Gorham Proverbs Test (Gorham, 1956) and the Social Comprehension Subset of the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1955). It includes five categories of thought disorder: (1) linguistic form and structure, (2) statement content, (3) intermixing, (4) relationships between questions and responses, and (5) behavior.

Impairment of executive functioning is also frequently reported in schizophrenia (Stratta et al., 1997). The Wisconsin Card Sorting Test (WCST) (Nelson, 1976) is one of the most widely used neurocognitive tasks for assessment of executive function, which includes working memory, abstraction, maintenance of set, and response to feedback. The task of the WCST requires a subject to sort a card with figures to one of four cue cards; the card can be sorted by either color, number, or form of the figures, but only one of these categories is considered correct on a given trial. Once the subject discovers the sorting principle, it shifts unexpectedly, and the subject must respond to the changing contingencies and infer the new correct sorting strategy. Numerous studies have reported poor WCST performance in individuals with schizophrenia. For example, Gold, Carpenter, Randolph, Goldberg, and Weinberger (1997) demonstrated that schizophrenic patients complete significantly fewer categories, and make more perseverative errors than normal controls. WCST performance in schizophrenic patients has been correlated with long-term social functioning and negative symptoms (Breier, Schreiber, Dyer, & Pickar, 1991). It has been reported that the WCST impairment in schizophrenia is present at the onset of the illness, and is neither secondary to previous neuroleptic treatment nor to chronicity of illness (Parellada, Catarineu, Catafau, Bernardo, & Lomena, 2000).

As noted earlier, although both positive thought disorder and impairment of executive function play important roles in the pathophysiology of schizophrenia, the association between them has not been fully investigated. It is challenging to examine whether there is a significant association between executive function and linguistically expressed thought disorder, since executive function, which also pertains to problem-solving ability, is known to be strongly related with social function (Reed, Harrow, Herbener, & Martin, 2002). Although, there have been several previous studies on the association between thought disorder and cognitive function in schizophrenia, they have not reached to clear conclusions regarding this association. Some studies reported a significant association between thought disorder and executive function in individuals with schizophrenia (Nestor et al., 1998), bipolar I disorder (Dixon, Kravariti, Frith, Murray, & McGuire, 2004), and schizotypia (Gooding, Kwapil, & Tallent, 1999). It has been reported that the P300

amplitude of event-related potentials in schizophrenic patients with positive thought disorder was significantly smaller than that in patients without positive thought disorder in some previous studies (Higashima et al., 1998; Iwanami et al., 2000; Laurent & Baribeau, 1992; McConaghy et al., 1993;). On the other hand, Sponheim, Surerus-Johnson, Leskela, and Dieperink (2003) presented that bizarre-idiosyncratic responses on Gorham's Proverb Test (Gorham, 1956) were not associated with cognitive function. Stratta, Daneluzzo, Bustini, Prosperini, & Rossi (2000) also reported a lack of significant correlations between WCST indexes and clinical assessment, including that of formal thought disorder using the Scale for the Assessment of Positive Symptoms.

The aim of the present study is to evaluate the association between positive thought disorder and impairment of executive function in individuals with schizophrenia. We hypothesized that more severe positive thought disorder would be associated with poorer executive function, since both positive thought disorder and impairment of executive function have been reported to be associated with poorer outcome in schizophrenia.

METHODS

Subjects

The subjects were 27 (15 males and 12 females) inpatients with schizophrenia diagnosed by *DSM-IV* (APA, 1994). All patients were biologically unrelated Japanese individuals. The following were the criteria for exclusion from the study: (1) history of head injury, (2) history of substance abuse or dependence, (3) serious medical illness, (4) age less than 20 or more than 60 years, and (5) acute phase of treatment. Written Informed consent was obtained from all the subjects after procedures have been fully explained to them.

Assessment of Thought Disorder, Executive Function, and Symptoms

Harrow's scale was used to assess positive thought disorder of the patients with schizophrenia (Harrow & Quinlan, 1985). After the interview was tape-recorded and typed verbatim by the same psychiatrist, thought disorder was scored by well-trained research psychiatrists, with discussion among them. Degree of thought disorder was evaluated by assigning scores of 0, 0.5, 1, or 3. The total score excluding the fifth category has been shown to be reliable in evaluating disordered thinking in the Japanese version (Saito et al., 1997;

Sugiura et al., 1995). The fifth category, which evaluates behavior, was not included in this study because we did not videotape the interview.

The WCST Computer Version-II Research Edition (Curtiss & Tuttle, 1993; Heaton, Curtiss, & Tuttle, 1993b) was used to assess the executive function. Number of categories completed and % perseverative errors (Nelson type) were used as parameters of executive function in this study.

IQ was estimated using Kaufman's short version with four subsets of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981): Similarities, Arithmetic, Picture Completion, and Digit Symbol. The validity of the short forms of the WAIS-R for testing of individuals with schizophrenia has been evaluated in Japanese subjects (Uetsuki et al., 2004).

The Magical Ideation Scale is a self-reported true–false scale with 30 items based on Meehl's description of magical ideation as a symptom of schizotypia, or schizophrenia-proneness (Eckblad & Chapman, 1983). All of the subjects completed this scale.

The severity of current symptomatology was rated with the Brief Psychiatric Rating Scale (BPRS) (Miyata, Fujii, Inagaki, Inada, & Yagi, 1995; Overall & Gorham, 1962), with 18 items, each rated 0–6. Symptoms were evaluated based on the total score of the BPRS and the two four-item symptom clusters reflective of positive symptoms (sum of the scores for suspiciousness, unusual thought content, grandiosity, and hallucinatory behavior) and negative symptoms (sum of the scores for motor retardation, blunted affect, mannerisms and posturing, and emotional withdrawal) of schizophrenia (Guelfi, Faustman, & Csernansky, 1989).

Socio-economic status (SES) was assessed using the Hollingshead Scale (Hollingshead & Redlich, 1958) SES was categorized from 1 to 5, with a smaller number indicating better SES.

Statistical Analysis

All statistical analyses were performed using SPSS for Windows (version 12.0.1, SPSS Inc., Chicago, USA). Demographic and clinical variables were compared between two groups with the Pearson Chi-square or Fischer exact tests in the case of qualitative data, and with the Mann–Whitney U-test for independent samples in case of quantitative data. Spearman's correlation analysis was performed to assess the relationships among demographic and clinical variables and neuropsychological findings. Partial correlation analysis, controlling for age, was also performed to assess the relationships among neuropsychological findings.

Table 1. Demographic and clinical variables and medications ($N = 27$)

	Mean	SD
Age (years)	41.5	10.1
Age at onset (years)	23.3	6.3
Duration of illness (years)	18.3	11.6
Number of past admissions (times)	3.2	1.9
Total duration of past hospitalization (months)	115.8	125.1
Duration of education (years)	12.9	2.3
Working time (years)	5.2	6.2
SES	3.4	1.2
Antipsychotics (equivalent to haloperidol mg/day)	21.4	18.0
Antiparkinson drug (equivalent to biperiden mg/day)	3.0	1.8
Benzodiazepines (equivalent to flunirazepam mg/day)	2.9	2.4
BPRS		
Total score	19.3	7.0
Positive symptom	5.2	3.4
Negative symptom	4.9	3.1

SD: Standard Deviation; SES: Socio-economic state (Hollingshead scale); BPRS: Brief Psychiatric Rating Scale, 0–6 range version.

Patients with a total score of more than three points on Harrow's scale were included in the Thought-Disordered (TD) group according to the manual for CIPTD (Marengo et al., 1986). Patients with a total score of less than three points on Harrow's scale were included in the Non-Thought-Disordered (NTD) group. As for executive function, patients with no category completed in WCST were included in the poor WCST group, while all other patients were included in the good WCST group. Differences in measurements between the TD and NTD groups and between the good and poor WCST groups were also evaluated by multivariate analysis of covariance (MANCOVA) using age as a covariate. Findings of $p < .05$ (two-tailed) were considered significant.

RESULTS

Demographic and Clinical Characteristics

During this study, all of the subjects underwent pharmacological therapy with conventional antipsychotics. Table 1 shows the demographic and clinical variables and medication status of the subjects. The subjects consisted of 7 paranoid subtype, 14 disorganized subtype, 1 catatonic subtype, 4 undifferentiated subtype, and 1 residual subtype. For four subjects (14.8%)

Table 2. Thought disorder and neuropsychological findings ($N = 27$)

	Mean	SD
Harrow's scale		
WAIS comprehension test score	3.5	4.2
Proverbs test score	3.2	5.0
Total score	6.7	8.8
WCST		
Number of categories completed	1.2	1.8
% perseverative errors	28.9	19.6
Estimated IQ	78.4	12.4
Magical ideation scale	11.4	4.6

WAIS: Wechsler Adult Intelligence Scale.
WCST: Wisconsin Card Sorting Test.

there was a history of schizophrenia in first- or second-degree relatives. Twenty-six of the subjects were right-handed and one was left-handed.

Thought Disorder, Executive Function, and Symptoms

Table 2 shows the severities of thought disorder and neuropsychological findings for the subjects. Five subjects (18.5%) had no positive thought disorder, as determined using Harrow's scale (i.e., total score on Harrow's scale was zero). Number of categories completed in the WCST was zero for all of the subjects with a family history of schizophrenia. There were no significant differences between male and female subjects in either WCST performance or scores on the Harrow's scale.

Relationships Between Neuropsychological Findings and Demographic Variables

Current age exhibited significant positive correlations with both estimated IQ (Spearman's $r = 0.46$, $p < .05$) and BPRS total score (Spearman's $r = 0.48$, $p < .05$).

Table 3 presents a partial correlation analysis, controlling for age, between neuropsychological findings and demographic variables. The WAIS comprehension test score on Harrow's scale exhibited a significant negative correlation with age at onset and a positive correlation with duration of illness ($p < .05$). Number of categories completed in the WCST exhibited a significant positive correlation with duration of education and a significant negative

Table 3. Partial correlations, controlling for age, between demographic variables and thought disorder, neuropsychlogical findings, and severity of symptoms ($N = 27$)

	Age at onset	Duration of illness	Number of admission	Duration of hospitalization	Duration of education	Working time	SES	Antipsychotics	Antiparkinson drug	BZs
Harrow's scale										
WAIS comprehension test score	−.40*	.41*								
Proverbs test score										
Total score										
WCST										
Number of categories completed					.71**		−.52**			
% perseverative errors	.54**	−.54**								
Estimated IQ					.64**					
Magical ideation scale	−.50**	.50**	.48*		−.41*	−.51**	.42*			
BPRS total score				.59**		−.46*				
Positive symptom				.48*		−.42*				
Negative symptom			−.53**	.48*						

*$p < .05$.

**$p < .01$.

SES: Socio-economicm state (Hollingshead scale); BZ: benzodiazepine; WAIS: Wechsler Adult Intelligence Scale; WCST: Wisconsin Card Sorting Test; BPRS: Brief Psychiatric Rating Scale, 0–6 range version; Antipsychotics: equivalent to haloperidol; Antiparkinson drug: equivalent to biperiden; BZs: equivalent to flunirazepam.

correlation with SES ($p < .01$). Percent perseverative errors on the WCST exhibited a significant positive correlation with age at onset and a significant negative correlation with duration of illness ($p < .01$).

There were no significant correlations between neuropsychological findings and medication status (daily doses of antipsychotics, antiparkinson drugs, and benzodiazepines).

Comparison Between TD and NTD Groups

The mean total score on Harrow's scale was 10.3 (SD 9.5) in the TD group (11 males and 6 females, mean age: 42.7 (SD 9.5) years) and 0.65 (SD 0.91) in the NTD group (6 males and 4 females, mean age: 39.5 (SD 11.3) years). There were no significant differences in age, sex, or family history of schizophrenia between the two groups. Percent perseverative errors on the WCST was significantly lower and magical ideation scale was significantly higher in the TD group than in the NTD group ($p < .05$) (Table 4).

Comparison Between Poor and Good WCST Groups

Since performance on the WCST was very poor in this study sample, subjects were divided by the number of categories completed into a poor WCST group ($N = 15$) and good WCST group ($N = 12$) (Table 5). The poor WCST group had more % perseverative errors on the WCST than that in the good WCST group, though the difference between groups was not significant (% perseverative errors: 36.2 (SD 23.9) in the poor WCST group; 19.7 (SD 4.5) in the good WCST group, $p = .19$; Mann–Whitney test). The poor WCST group had significantly less education, lower SES, and lower estimated IQ ($p < .01$).

Relationships Among Thought Disorder, Results of WCST, and Severity of Symptoms

Table 6 presents partial correlations, controlling for age, among the results on Harrow's scale, WCST performances, estimated IQ, magical ideation scale, and BPRS. There was a significant positive correlation between WAIS comprehension test score on Harrow's scale and positive symptoms of BPRS ($p < .05$). Estimated IQ exhibited a positive correlation with a number of categories completed in the WCST ($p < .01$) and a negative correlation with % perseverative errors on the WCST ($p < .05$). There were no significant correlations between the scores on Harrow's scale and parameters of WCST performance.

Table 4. Comparison between TD and NTD groups

	TD ($N = 17$)	NTD ($N = 10$)	F	p
Age (years)	42.7 (9.5)	39.5 (11.3)	—	—
Age at onset (years)	22.1 (5.6)	25.2 (7.0)	1.7	.21
Duration of the illness (years)	20.7 (10.0)	14.3 (13.4)	1.8	.19
Number of past admission (times)	3.5 (2.2)	2.6 (1.2)	0.96	.34
Total duration of past hospitalization (months)	143.5 (122.3)	68.7 (121.3)	1.7	.21
Duration of education (years)	13.1 (2.7)	12.6 (1.4)	0.22	.65
Working time (years)	3.3 (2.4)	6.7 (4.5)	0.97	.33
SES	3.5 (1.5)	3.1 (0.57)	0.63	.44
Antipsychotics (equivalent to haloperidol mg/day)	25.3 (19.9)	14.7 (12.2)	1.7	.20
Antiparkinson drug (equivalent to biperiden mg/day)	3.2 (2.2)	2.4 (3.1)	0.60	.45
Benzodiazepines (equivalent to flunirazepam mg/day)	3.2 (2.1)	2.7 (1.1)	0.86	.36
BPRS total score	20.2 (6.8)	17.7 (7.4)	0.71	.41
Positive symptom	6.1 (3.0)	3.5 (3.5)	3.3	.080
Negative symptom	4.2(3.4)	6.0 (2.4)	1.5	.23
WCST				
Number of categories completed	1.4 (2.1)	0.80 (1.1)	1.8	.19
% perseverative errors*	21.8 (13.2)	40.8 (23.3)	7.7	.010
Estimated IQ	80.9 (11.5)	74.1 (13.2)	1.3	.27
Magical ideation scale*	13.0 (4.6)	8.6 (3.3)	6.0	.022

Mean (SD).

*$p < .05$; MANCOVA with covariate of age.

TD: Thought-disordered (total score of Harrow's scale ≥ 3); NTD: non-Thought-disordered (total score of Harrow's Scale < 3); SES: Socio-economic state (Hollingshead scale); BPRS: Brief Psychiatric Rating Scale, 0–6 range version; WCST: Wisconsin Card Sorting Test.

In addition, analyses controlling the duration of education or estimated IQ were performed, since the poor WCST group had a significantly lower educational level than the level of the good WCST group, and similar results were observed.

In the good WCST group, % perseverative errors on the WCST exhibited strong significant negative correlations with Proverbs test score ($r = -0.96$, $p < .001$) and total score ($r = -0.87$, $p < .001$) on Harrow's scale after controlling for age (Table 7). The correlations between % perseverative errors on the WCST and Proverbs test score and total score on Harrow's scale remained significant after controlling for age and the duration of education or age and estimated IQ ($p < .01$).

In the poor WCST group, no significant correlations were found between Harrow's scale scores and % perseverative errors on the WCST (Figure 1).

Table 5. Comparison between poor and good WCST groups

	Poor WCST ($N = 15$)	Good WCST ($N = 12$)	F	p
Age (years)	43.3 (7.8)	38.9 (12.3)	—	—
Age at onset (years)	23.3 (7.0)	23.3 (5.4)	0.003	.96
Duration of illness (years)	20.1 (12.2)	15.7 (10.6)	0.004	.95
Number of past admissions (times)	3.7 (2.0)	2.6 (1.6)	1.2	.29
Total duration of past hospitalizaiton (months)	160.1 (141.7)	60.4 (73.7)	3.1	.091
Duration of education**(years)	11.5 (1.2)	14.6 (2.2)	23.2	<.001
Working time (years)	4.1 (4.9)	6.6 (7.6)	1.3	.26
SES**	3.9 (1.0)	2.7 (1.2)	8.9	.006
Antipsychotics (equivalent to haloperidol mg/day)	23.9 (16.1)	18.2 (20.4)	0.26	.62
Antiparkinson drug (equivalent to biperiden mg/day)	2.7 (1.4)	3.3 (2.3)	0.43	.52
Benzodiazepines (equivalent to flunirazepam mg/day)	3.2 (2.5)	2.5 (2.2)	0.84	.37
BPRS				
Total score	20.8 (6.5)	17.3 (7.3)	1.6	.22
Positive symptom	5.5 (3.9)	4.7 (2.8)	0.013	.91
Negative symptom	5.5 (3.4)	4.3 (2.7)	1.7	.20
Harrow's scale				
WAIS comprehension test score	3.9 (5.3)	3.0 (2.3)	0.25	.62
Proverbs test score	4.0 (5.7)	2.2 (3.9)	0.61	.44
Total score	7.9 (10.8)	5.2 (5.6)	0.47	.50
Estimated IQ**	74.3 (10.6)	83.5 (13.1)	12.7	.002
Magical ideation scale	12.5 (5.5)	9.9 (2.8)	1.4	.25

*$p < .05$.

**$p < .01$; MANCOVA with covariate of age.

WCST: Wisconsin Card Sorting Test; poor WCST group: no category completed on WCST; good WCST group: number of categories completed on WCST ≥ 1; SES: Socio-economic state (Hollingshead scale); WAIS: Wechsler Adult Intelligence Scale, BPRS: Brief Psychiatric Rating Scale, 0–6 range version.

DISCUSSION

In the present study, no significant correlation was found between the severity of positive thought disorder and impairment of executive function in the subjects with schizophrenia; however, the TD group had significantly lower % perseverative errors than the NTD group. Furthermore, there were strong significant negative correlations between % perseverative errors and severity of positive thought disorder in the good WCST group.

Table 6. Partial correlations, controlling for age, among Harrow's scale, WCST performance, and severity of symptoms ($N = 27$)

	Harrow's scale			WCST				BPRS		
	WAIS comprehension test score	Proverbs test score	Total score	Number of categories completed	% perseverative errors	Estimated IQ	Magical ideation scale	Total score	Positive symptom	Negative symptom
Harrow's scale										
WAIS comprehension test score		.86**	.96**						.41*	
Proverbs test score			.97**							
Total score										
WCST										
Number of categories completed						.63**				
% perseverative errors						−.40*				
Estimated IQ										
Magical ideation scale										
BPRS										
Total score									.81**	.55**
Positive symptom										
Negative symptom										

*$p < .05$.

**$p < .01$.

WCST: Wisconsin Card Sorting Test; WAIS: Wechsler Adult Intelligence Scale; BPRS: Brief Psychiatric Rating Scale, 0–6 range version.

Table 7. Partial correlations, controlling for age, among Harrow's scale, WCST performance, and severity of symptoms in the good WCST group ($N = 12$)

	Harrow's scale			WCST				BPRS		
	WAIS comprehension test score	Proverbs test score	Total score	Number of categories completed	%perseverative errors	Estimated IQ	Magical ideation scale	Total score	Positive symptom	Negative symptom
Harrow's scale										
WAIS comprehension test score		.61*	.85*					.66*		
Proverbs test score			.94**		−.96**			.70**		
Total score					−.87**			.76**		
WCST										
Number of categories completed						.61*				
% perseverative errors								−.62*		
Estimated IQ										
Magical ideation scale								.74**	.77**	
BPRS										
Total score									.77**	.64*
Positive symptom										
Negative symptom										

*$p < .05$.

**$p < .01$.

WCST: Wisconsin Card Sorting Test; good WCST group: number of categories completed on WCST ≥ 1; WAIS: Wechsler Adult Intelligence Scale; BPRS: Brief Psychiatric Rating Scale, 0–6 range version.