Chronic adminis ra ion of clo apine alle ia es re ersal-learning impairmen in isola ion-reared ra s

Nanxin Li[a], Xihong Wu[a] and Liang Li[a,b]

Isolation rearing has been used for inducing schizophrenia-like symptoms in rats. Human schizophrenics have deficits in prefrontal-dysfunction-related cognitive/behavioral flexibility. Rats with lesions of the medial prefrontal cortex perform poorly in reversal learning. It is uncertain whether isolation rearing, however, causes reversal-learning impairment in adult rats. Using the rotating T maze, this study examined the effect of chronic administration of clozapine on visual discrimination learning and reversal learning in isolation-reared and socially reared adult rats. The results show that isolation-reared rats without clozapine injection performed significantly worse than socially reared rats in reversal learning but not in acquisition learning. Chronic injection of clozapine (5 or 10 mg/kg) in isolation-reared rats significantly improved reversal learning but had no effects on acquisition learning. Further data analyses show that in both the inhibition phase and the new-strategy-acquisition phase of reversal learning, isolation-reared rats needed significantly more correct-response trials to reach the criterion than socially reared rats, and clozapine significantly reduced the isolation-induced impairment of reversal learning only in the new-strategy-acquisition phase. In socially reared rats, clozapine had a dose-related interfering effect on reversal learning but not acquisition learning. This study supports the use of isolation rearing as a model for investigating the neurodevelopmental hypothesis of schizophrenia. ***Behavioural Pharmacology*** **18:135–145 © 2007 Lippincott Williams & Wilkins.**

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In rod c ion

s s s t t s s ss t t t st s t t s' t ('C tt , 1996; , 1996; E C s, 1998; , 2000; G t *et al.*, 2003; T *et al.*, 2004; B , 2005; F st *et al.*, 2005; s, 2005). T t t , s t t s , s ts t t t t t . t s s t st t (1987), s t t t t , t ts t s s t t t t t s. T s t t s s s s s t t t t t s s st t s ss s t t . s t t s t t s s . t t t s, s , , s t s t s t s t s t s (, 2006). T s, st s t t t s s t t st t t s s s -

t s t s st s (H *et al.*, 2000; ss F , 2001; *et al.*, 2002, 2003; B s *et al.*, 2003; , 2006; *et al.*, 2006). ts, s t , t s st t s t t s ss (s *et al.*, 1991, 1992; t A t *et al.*, 2000; H *et al.*, 2001; D *et al.*, 2002; *et al.*, 2003; B *et al.*, 2004; H t *et al.*, 2004; *et al.*, 2004; *et al.*, 2005) t s (s *et al.*, 1991; G *et al.*, 1993; s *et al.*, 1994; s , 1997; s *et al.*, 1998; t G , 1998; *et al.*, 2000; t *et al.*, 2000; , 2001; ss *et al.*, 2001; A , 2005) s .

t ts s s t / s t (t s t s t s t), s t st t t s s C t T st (C T) (. . , 1963; s , 1983; s *et al.*, 2002; tt *et al.*, 2004; T *et al.*, 2006), , t s s , t t ss s s (s C , 1997). F , t C T, st s t t t s t (s *et al.*, 1989; s *et al.*, 2000; D s, 2003; *et al.*, 2005), t ts t s t t s t s t t s s t t t . B *et al.* (2006) t t t t 4 26 s (t t s - t) t t t, s t C T (s t ts, s t s, t t s) s t 54 t ts t s - t st .

s, s , s s t t t s st t t s st t , s t s t st t / t (, 1965; t s H t , 1969; s *et al.*, 1991; H t G t , 1998; , 1998; A *et al.*, 2003, 2006; ss *et al.*, 2003; *et al.*, 2003; C- *et al.*, 2004, 2005; s *et al.*, 2005). ts, s ss s s t t t t (FC) t t t t (FC). D t t t ts' t FC (s ss s t t s t t t t s) s s (s t s t) t t s t (, 1998; C s s, 2003; *et al.*, 2004). D t t FC s s s t t s t (*et al.*, 2002; C s s, 2003; A- B , 2003). A-t FC s ts FC ts t s s t t s, FC s ts t s s ss t st s ss t FC s ts t s t st s ss t (C s s, 2003). t (C), D- t , 801, ts t t s, t s t t FC, s s ts' s (ts T , 2001; A *et al.*, 2003, 2006; *et al.*, 2003; s *et al.*, 2005; s, 2005). C - t s s tt t t t t s t s, s s , s , (A *et al.*, 2003, 2006; s *et al.*, 2005).

t st *et al.* (1997), t s s st t t -t -s t s t t -t -s t t t t -t -s t .T s ts s t t ts t FC s s t t - t t s t -t - s t t t -t -s - . *et al.* (1997) s st t t t ts FC s ts t t st t , t t s t t t s s t C T.

t s t , , t s t s, s t , t t s s t ts (*et al.*, 1962; s *et al.*, 1991; t s , 1996; , 2001; A *et al.*, 2003; *et al.*, 2004). F , s st s t t t s t s t t t s s t (*et al.*, 1962; s *et al.*, 1991; *et al.*, 2004). t st s (2001) A *et al.* (2003), , t s t s s t s t . , t st t s (1996), t s t s s t s t - ts t s t s. T s, t s ss t t t ts s t s s s - t t st s. As ts s t t s t t t FC (s *et al.*, 1991, 1992) s s t FC t t t t t s (, 1998; C s s, 2003; *et al.*, 2004; *et al.*, 2004), t s st s t t t t s s t s s t t FC s (, 1998).

As t t t s t , s s t t t s s' t s t s (t , 1989; D t *et al.*, 1991; *et al.*, 1991; *et al.*, 1992; ts F , 1992; t G , 1999; *et al.*, 2003; G t- *et al.*, 2005) ts' s ts (G , 1993; t H s, 1995; H t *et al.*, 1997; C *et al.*, 2001, 2005; B tt *et al.*, 2006; C st , 2006; t -A- *et al.*, 2006). T t s t s t s t t t s - t t s t / s (*et al.*, 2002; s, 2005). t s t , , t s t - - ts s (*et al.*, 1962; s *et al.*, 1991; *et al.*, 2004) t t t t . A t t st A *et al.* (2003), C s t s - t - s ts, t t t t s t s (2.5 / , t t t) s s t C - - t s ts t t s t - ts.

T t s st s t t ts st t s s t (s t) s t ts t t t s t -

. B t s t s - t st t t T (, 1998).

Me hods

Par icipan s

F t - t -D ts 21 s (t) s t B t E t A s T t . (B , C). T ss t t s: t s t - (24 ts) t s (24 ts). E t t s s t t t s s t t t s s (s).

F s t - ts, s s s t s t st (48 × 30 × 18). F s ts, t s s . As t s t s ts t t s , s t ts , s s t ts. A ts ss t (B t E t A s T t ., B , C) t . T t t t st t t t 24°C (2°C), t 40 50%, 12 t/ (ts 07.00). s t (2 s t st), ts t - t 85% t - t. T t s t st t t t , t t t 240 260 t t t t st .

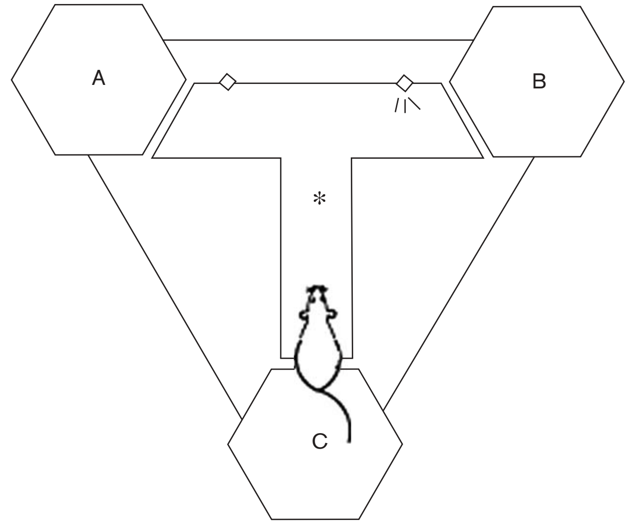
A ts t s t s t s ss t s t t . T ts t t t s t B t A C t , t s t C C A C , t s t s A s H s s s s t t s 1995.

Ro a ing T ma e

F 1 s s t t t t T s t s st . T t t T s s s t s (, 1998). B , t t s T t . T s st ss-st s s. t s t s s t t s t T t . T t s s t s A, B, C, s t . T t s 9.0 . E t t t t T t .

T T t s s s. T t s 13.5 t ts st . T st t t 7.3 t t 22.0 . As t T

Fig. 1



Overhead schematic view of the rotating T maze used for visual discrimination tests. The maze has (1) three hexagonal boxes (box A, box B, and box C), and (2) a T tunnel. In this figure, box C represents the start box, and the entrance of the T tunnel is connected to box C. A light spot is on the right side of the front wall of the T tunnel. The position of the axis of the T tunnel is indicated by the asterisk.

t t t ts s (s s t s s s st s F . 1), t t t t T- t st t t t ts t T-t s t t t t . t t (25.5 t) t T t , t t s (1 t , 8.5 t t). A t tt (ED) s st s t s, s s .

Vis al discrimina ion learning and re ersal learning

t t t (8 s s s t s t - ts), ts st t t t t t s s t ED(s) t T . A t sts t t t s .

D t st 3 s t , t s t t t 30 s s , t s t , t t EDs , ts t t s.

t t , ts t t s t t st t s. t , t t st s s s t s t t s t T t . F t ts, t t t s s t t t t s t , t t ts, t t s t t t s t t t . A t t t st t s , t t st t t t t s t s t t t t t . t t st t t t t (t s s '), t s t t (50 , B t E t A s T t ., B , C). t t t t s t t t t t (s s '), t .T t t t t s t s , t T t s t t t t t t t s , t t st t t t t . T t s s t , t st t . T s, t -t t st s s .

A t t 12 t s t t. T s s t t st t 2 s t ts t s t t , t t s 11 t t s t 12 t s t s t s.

t t t s t , t t t st s t t . s , t t t t s s t s s t , t t t t st s t s s , t t s s t ' (') ss t ' (t ') ss - t , s .

A t t s st s (. . t s H t , 1969; s *et al.*, 1991; *et al.*, 2002; C s s, 2003), t t t s , ts st st t t s- st t t t st t . t s st , t s t t t t s t t s (50% t) t s ss s, t s- st t s (t s t) s t .T s, t t's s - s t t s s: ( ) t t s ( ) t -st t - s t s .

Clo apine adminis ra ion

C- (-A- C t , t s, A) s ss t s s t , s H s st t t t 10 / H. C st t s t s t st t (6 8 s,). t s s t s s s s st s (. . G , 1993; s *et al.*, 2005; A - *et al.*, 2006), t s st t s t s 0, 5 10 / (t t st t t 0.1). T s, s t - ts s ts t t t s . F t, t t s st t t t t 30 tt t t t t .

S a is ics

A t 2 (t : s , s t) 2 (s tt ss s t s : t/ , / t) 3 (s : 0, 5, 10 /) t - s s s s t s st . G s t st s t - s s (A As). T s s s 11.5 s t (C , s, A). t s s t t 0.05. As 's t st s s t s s t s s t st st t st- t sts, t s st 's t st s s t t s s s t s.

Res l s

Original is al discrimina ion learning (acq isi ion learning)

A t ts s t s st t t s s t , t t t t s t t t t st s ss s t t t ss ts. F 2 s s t s t s s s t t t ( ) t s s t t ( ).

F t t t- s s t s t - s s t s t t t , A As s t t t ts t t s t t t s s s t ($P > 0.05$).

Re ersal learning

A t ts t t t s , t t s t t t t st s ss s ss ts. F 3 s s t s t- s s t s t t ( ) t s - s s t s t t t ( ). s-, ts t s t t t s t s s t . t , s t - ts t t t s t t s t t t t s s.

F t t- s s t s t t t , t t t t t s

t -s t t s t t

t t . s , s t - ts t

t t s 5 / s t-

t t -s t t t t

s ts t t (5 /)

$F(1,14) = 12.08$, $P < 0.001$. T t

s t - ts s ts t t

t s 10 / , , s t

s t, $P > 0.05$.

t A As -s s t t s t -

ts, t s s t t s

$F(2,21) = 123.14$, $P < 0.001$. 's st- t sts

s t t t t s s t-

t t .T s 5 /

t t- t t t s

10 / s t - ts (F . 3,).

t st , s ts, t s -s

s t t s , $F(2,21) = 8.71$,

$P < 0.01$. 's st- t sts s t t t

0 / t 10 / s t-

t. T 10 / t st

t- s s t -s t t t

t t s T 4T 41270.4(s82 6(104 s)-690.34)-71.1(.)-

F 56.60(60.263)-438.-1. - s8.-1. 2-359.26 s, t

As t t t t t

s s s t, t s t - A As

. T s s t t t s

s t t s t - ts

s ts t t s $F(1,14) = 246.73$,

$P < 0.001$, t t t s t - ts t t

t s t- t

s - t - ts - t
s - - ts (F . 4, -). A 2 (t)
3 (- s) A A s t t t t t
t t t t s s s t $F(2,42) = 83.85$,
$P < 0.001$ s t t t
$F(1,42) = 56.34$, $P < 0.001$ t t
- s $F(2,42) = 42.96$, $P < 0.001$.

F s - t - ts, 's st- t sts s
t t - t t s s s t- t

Disc ssion

As t t t , s st s t t t t t s t s t (, *et al.*, 1962; s *et al.*, 1991; t s , 1996; , 2001; A *et al.*, 2003; *et al.*, 2004), t t t t s t s s t t t st. H , s t t t s t t t T s t s st s s s t s t s t ss t t t t t st t t s t s .

F st, s t t s, t ED s t t s t t st t st s ss . s t, ts t t t t s t t t’ t t , t t t s s t s. t , s t sts t t t t , t t t s, s s s t ts, t t st ts t s t st s ss . , t st s ss , s s s s t st t , t t t , t t , s (t) s . F , s t t t T t t t s t s t t , s - t s . T , s t t t T , ss s t ts t s t t s t t st t s, s s t s , s t , t t T ( ) , s st t .

T s ts t s st s t t t t s t t s t ts s t t s s s t , s t - ts, t t t t , s t- t- s s t s t s ts t t t s .T s s s t t s ts *et al.* (1962), s *et al.* (1991), *et al.* (2004), t t t s t s .

t s st , , t t’s s t t s s t t t t - s s t s, t t s t s s t s t.T s, t s - t - s t t t t- s s t s s s st t s - ts t s t t t t t - s s t s. t s t t t t s s t t - s t s t - s s t s s s t st t ss t t . t

t s st t (s t t s t s st), s s ss s t t t ss ts, t - s t t t s - s s t s ss ts .

T t s t s , s st st s ss s- st t - s t st s st t s (t s H t , 1969; s *et al.*, 1991; *et al.*, 2002; C s s, 2003).T s ts t s st t t t s t - ts s s t s t t t s (t s) s , t t t- s s t s t t t s- st t . C st t , , t t t s t - - t t t s s . t -st t - s t s s , s t - ts t t t s t- t- s s t s t t t t t s t - ts t t s ts. T s, s t s t t s t t t s t -st t - s t s s , t t t t -st t - s t s .

t s s t t t FC t s t s ts t st t s T (, 1998). , t st C s s (2003), s t s s t t FC s ts’ t - st t - s t s s , s st t t t t FC s t s- st s ss t . t s s t FC s ts’ t t s s , s st t t t FC s s ss t s- st - s ss t . T s ts s t s st t ss t t s - t s t t FC t FC. t , t s ts s s ts t -st t - s t (- t) s s st t t t s t - - t s- ss s, s s t - t t t s s , ss t t t FC.

t s t t s t s s s s t t FC, ss (D - s *et al.*, 2006), s t s t s t s (*et al.*, 2003, 2004), t 5-HT s (C s et al., 1992; B et al., 1993; D et al., 2002), t 5-HT (et al., 2002), t (s et al., 1991; et al., 2002; E s et al., 2006), s 5-HT $_{2A}$ t -s t s t s s 5-HT $_{1A}$ t -s t s t s (et al., 2004), s s s t st t t t t t (t s 'D , 2005). T t s t s t s t t t s t - - t t s t t s t s .

G s s t t t t s t s st s t t s t s t t s s s (. . B et al., 1993; F et al., 1996; t -A t et al., 2000; D et al., 2002; s, 2005). C- s t t t 5-HT $_{1A}$ 5-HT $_{2A}$ t s. 5-HT $_{2A}$ t s s t t s t t s (t , 1989; et al., 2001; B t - et al., 2004; et al., 2006). T , t t t 5-HT $_{2A}$ t s t FC t s t s ss t s s ts t s t ss t t ts. A 5-HT $_{2A}$/ D_2 t t t s t t s ss t t- t t s t s s (A-t et al., 1986).

t t t s ss t FC, s t s s t s ss t st t s, t s s, st t , s, (. . s et al., 1992; H et al., 2001; D et al., 2002; et al., 2003; B et al., 2004; H t et al., 2004; et al., 2004; et al., 2005). T st s et al. (1991) s t t t t s , s t- , s s s t - ts. t , t st H et al. (2002) s t t s t s t t N- t -D- s t t - t s t (DA $_{1A}$) t st t t t , t s t s t t s. s- , t t t s - t - - s / t s ss ts s t s ss st t s s s t s s ss t t st s 's' t.

s t - t ts s s s t s- t ( ) (C et al., 2001, 2005; G et al., 2001; et al., 2001; ss F , 2001; B s et al., 2005), s t t t s t t t ts st - t s (C et al., 2001, 2005; G et al., 2001; et al., 2002). s t t st t t t s st st s s st s s s s s - t t (s , 2002). st s t t t s t ts t s (s s B et al., 2001; G et al., 2001; et al., 2001; ss F , 2001; B s et al., 2005) t t- s t s, s , ts t s t ts (et al., 1999, 2000, 2002; et al., 2002; et al., 2002). T - , t s s s t - - - s s t t t t / t t s t t t st s.

t s st , s ts, t s (10 /) s t t -st t - s t s t t t t s s .T s t s st t t t t t s s .T st H et al. (2001) s t t s ts, (5, 10 / , s t s-) s t- s - t s t t FC. T s, t s s t FC t t s t s t t t t -st t - s t s s s ts. , t t s t t t t st t s s s t FC t t t t t ts (et al., 2000) t -st t - s t s s s t t t s ss t t .

s , t s ts t s st t t t s t s t t s , t t s t , s s s t t ts. s t - ts, t t t t s t -st t - s t s , t t t t s , s t st t , t st t - s s ts s t -st t - s t s s ts. T s, t s st s t s t st t t s t t / t st t t t s t s.

Ackno ledgemen s

T s s s t t s t s t's s F s t , t t st E t C (t . 02170), s t 985' t.

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