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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Keywords: animal model, clozapine, isolation rearing, rat, reversal learning, schizophrenia, T maze

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In rod c ion

si i s s t t s i i is ss i t it t i ist s t t i i i i 's' t ('C tt , 1996; i , 1996; E C 's, 1998; i , 2000; G t *et al.*, 2003; T i i *et al.*, 2004; B , 2005; F st *et al.*, 2005; s, 2005). T t t , i is t i i 'i t i s i i , s its t- i ti t it i 't . t sis t . st ti i (1987), i i i i s i t t . t t it , t ts t i i s i si t ti t t t s. T is - t sis s i i si s t t ti -'i i t t s s st ti i s ss s i t- ti . N si 'i i t t s t 'iti s i s i i- t i s. it t t 's, si ', , is 'i t s t s- ti s i i ti s t t s i i (i , 2006). T s, st 'is t i t - t 's i t i 's is iti i sti ti t is s i s i i- t s t s i ist s (H i *et al.*, 2000; iss F , 2001; *et al.*, 2002, 2003; B s *et al.*, 2003; i , 2006; i *et al.*, 2006). ts, i is ti i , t s st ti s i t t s issi (s *et al.*, 1991, 1992; it - A iti *et al.*, 2000; H i *et al.*, 2001; D *et al.*, 2002; i *et al.*, 2003; B *et al.*, 2004; H t *et al.*, 2004; *et al.*, 2004; *et al.*, 2005) i 'iti s (s *et al.*, 1991; G *et al.*, 1993; i' i s *et al.*, 1994; s i , 1997; s *et al.*, 1998; V t . G , 1998; L i *et al.*, 2000; V t *et al.*, 2000; i , 2001; iss *et al.*, 2001; A , 2005) s .

i i ti ts s s iti / i s ti (i' t s it - i s' s ti t s ti), i is ti sti t t is si C ti T st (CT) (. . i , 1963; is , 1983; L s *et al.*, 2002; itt *et al.*, 2004; T *et al.*, 2006), s i , t is s , t ti ssi s s (i s C i , 1997). F , i t CT , i is t i s t i t t s ti (s *et al.*, 1989; s *et al.*, 2000; D is, 2003; N *et al.*, 2005), ti ts it s i i ati t s t s i t t s s it ti . B *et al.* (2006) t t t t t 4 26 s i i (t i ti s - ti) t t t, s i t CT (s t its, s ti s, t t s) i si i t i t 54 ti ts it s i - i t st .

i 's, s i , i i s i 's t t i i it t i s i i st t i t i s i i st t , is t s t sti iti / i i i it (i , 1965; i t s H t , 1969; s *et al.*, 1991; H t G t , 1998; Li , 1998; A - i *et al.*, 2003, 2006; ssi *et al.*, 2003; *et al.*, 2003; C *et al.*, 2004, 2005; is *et al.*, 2005). ts, s ss s - s t t i t t (FC) t it t (FC). D t t i i i t i i ts' t FC (i is ssi s t t s t t t i i t s) i i s s (s ti s ti) t t isiti i (Li , 1998; C s i s, 2003; *et al.*, 2004). D t t FC 's i i s s t t isiti i (*et al.*, 2002; C s i s, 2003; A B , 2003). A t FC- si ts FC- si ts it si s t t 's, FC- si ts it s i s ssi t i s sti s ss i ti FC- si ts it s i i t sti s . ss i ti (C s i s, 2003). ti i i (C), D- t i , 801, i ts t ti s, ti s t i i t FC, si i i t i i s ts' s - i (ts T , 2001; A - i *et al.*, 2003, 2006; *et al.*, 2003; is *et al.*, 2005; i s, 2005). C -i i i t . s i si i t tt t i ti t i ti s ti s, s s i , i si , i (A - i *et al.*, 2003, 2006; is *et al.*, 2005).

t st *et al.* (1997), t s sist t t -t -s t i i s t t -t -s t i i t t t -t -s t i i . T s ts s t t ts it FC si s i t i it i i i - t t s i s t t -t - s t t t -t -s - . *et al.* (1997) s st t t t i i ts i FC- si ts t i i t i i i st t , t t s t t s is t CT .

t s t , , t is ti i i i s, s t , i it t s s i i t ts (*et al.*, 1962; s *et al.*, 1991; it s , 1996; . , 2001; A - i *et al.*, 2003; *et al.*, 2004). F , s st i s t t t is ti i i i s i t i t t t i i is js i i ti (*et al.*, 1962; s *et al.*, 1991; *et al.*, 2004). t st i s (2001) A - i *et al.* (2003), , it isiti i s i s t is ti i . , i t st it s (1996), t isiti i s i is t i i is ti - ts it s i t 's. T s, it is ss t t t ts is ti i s i si is - t t sti i s. As i ts is ti i 't s i ti it i t FC (s *et al.*, 1991, 1992) si s t FC i it t t t 't i i s i (Li , 1998; C s i s, 2003; *et al.*, 2004; *et al.*, 2004), t is st s i t t i i t t i i i t si s t s i s t t FC s i (Li , 1998).

As i i t t i ti s ti , i s i s t it t s i i s' iti s t s (t , 1989; D t *et al.*, 1991; *et al.*, 1991; i *et al.*, 1992; ts Fi i , 1992; t G , 1999; *et al.*, 2003; G t *et al.*, 2005) ts' s i i - i i i i ts (G , 1993; V t Hi i s, 1995; Hit *et al.*, 1997; Ci i *et al.*, 2001, 2005; B tt *et al.*, 2006; L i C ist , 2006; t -A *et al.*, 2006). T i iti s i t i s t s i t t i i ti s i i - t i iti s iti / i i i i s (*et al.*, 2002; i s, 2005). t is t , , t is ti - i -i i i ts . s i (*et al.*, 1962; s *et al.*, 1991; *et al.*, 2004) i t i t t t it i . A i t t st A - i *et al.* (2003), C i i s i i t is - ti - s i ts, t t t i ti s ti i si (2.5 / , i t it t) si i i t s t C -i i i - t i s i ts t t i is ti - ts.

T i t is st s t i t ts i i ist ti i i i is is i i ti i (isiti i) s i i t ts it it t is ti - i i . B t isiti s - i t st i t ti T (Li , 1998).

Me hods

Par icipan s

F t - i t -D ts 21 . s (t) s t B ri Vit i E i t A i 's T Lt . (B ri , C i). T ssi i t t i s: t is ti - (24 ts) t s i (24 ts). E t t i . s s t i i i t t s s i t it i t s s i (s).

F is ti - ts, i i i s s i si t s t sti (48 × 30 × 18). F s i ts, t i i i 's s i . As t is t s i ts t i t s , is t ts t , s . s t ts. A ts ss t (B ri Vit . i E i t A i 's T Lt ., B ri , C i) t . T i t i t iti st t t t 24°C (2°C), i it 40 50%, 12 i t/ ('i ts 07.00). i s t i (2 s t sti), ts i t i- t 85% t - i i t. T i t s t st i ti t t , it t t 240 260 t t ti t sti .

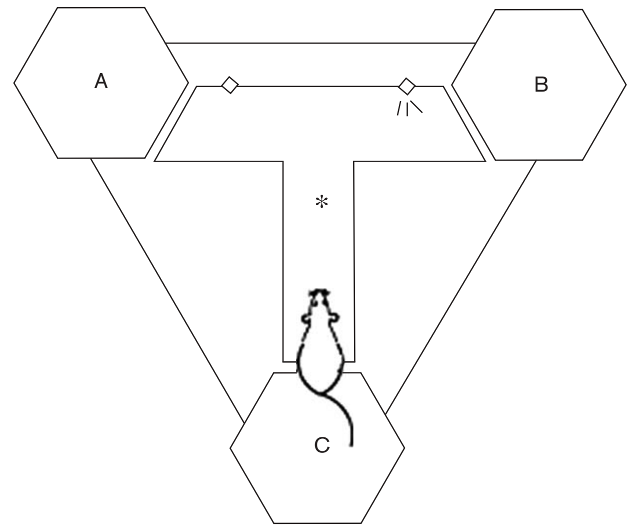
A ts t i i i i 's i t s t i 's ss t 'i s i ti i t T i ts . i t i t t i 'i s t B ri L t A i C t , t i 'i s t C i C i A i C , t 'i i s t Us A i 's H s i N s i s is t i t N s i i 1995.

Ro a ing T ma e

Fi 1 s s t i t t ti T s i t is st . T t ti T s 's s i i t i 's (Li , 1998). B i , t t s T t . T s st i ss-st i s s. U t s t i s 'i s t t s t T t . T t s i s t s A, B, C, s ti . T t s 9.0 . E t t t t T t .

T T t s 's i s. T t s 13.5 t its st T st t i t 7.3 t t 22.0 . As t T t its is (s siti is s s st is i Fi . 1), t t t t T - t st it t t its t T -t s t t t . t t (25.5 i t) t T t , t t s (1 i i t , 8.5 t t). A 'i t itti i (LED) s i st i si t s, i i is s .

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.

Vis al discrimina ion learning and re ersal learning

t i t t i (8 s s i is ti is ti - ts), ts st t t i t i i i i i t 'i t s s t LED(s) i t T . A t sts t i t 'i t s .

D i t i st 3 s t i i , t s t i t t 30 s i si , t s i t , t t LEDs , ts i t t s.

t t , ts t i t s i t st t i s. t i , t 'i t sti s s s t si t t s t T t . F t ts, t t 'i t si s t t t t t s it , t t ts, t t si it t 'i t s t t t . A t t st t s , t t st t t t t s t ꞈ ˀ s t ꞈt t t t ꞈiꞈ . t t st iꞈt t t t (ʻ t s . ꞈs ʼ), it s it ʻʻ t (50 , B ꞈiꞈ Vit ˀ i E i ꞈt ˀ Aꞈi ˀsT ꞈ ˀ L t ., B ꞈiꞈ , C iꞈ). t t ꞈt t sit t t t t (ꞈ ʻ s ꞈs ʼ), it i ꞈ T t t iꞈ ˀ ꞈt iꞈiꞈ t t s t ꞈ ˀ s , ꞈ t T t ꞈꞈ ˀ s t t it t ꞈt ꞈ ꞈꞈ tiꞈ t t is , i t ꞈ t st t iꞈ t ꞈ t t i ˀ.T i t s ꞈ s ˀ t , ꞈ t i ˀ st t .T s, ꞈ ꞈ ti ꞈ-t i ˀ t stiꞈ s s .

A t t ˀ 12 t i ˀs i t t. T is is i iꞈ ti ꞈ t iꞈiꞈ ˀ st i t ˀ 2 s ꞈtiˀ ts t isiti ꞈ-ˀ ꞈiꞈ it i ꞈ, t t is 11 t t i ˀs t 12 t i ˀs t ꞈs ti s.

ꞈ t t it i ꞈ isiti ꞈ ˀ ꞈiꞈ , it ꞈt t st s ˀ ˀ ꞈiꞈ ꞈ t ꞈ t . ꞈ s ˀ ˀ ꞈiꞈ , t ꞈ t it i ꞈ iꞈ t s s t s iꞈ isiti ꞈ ˀ ꞈiꞈ , t t t t sti ˀ s ꞈtiꞈ ꞈ s s , t t is i s "i t ʼ (ʻ ꞈ ʼ) ss i ti ꞈ ʻ ʼ ("i t ꞈ ʼ) ss i- ti ꞈ, i s .

A iꞈ t t i s st i s (. . iꞈt s ꞈ H ˀ t , 1969; ꞈ s *et al.*, 1991; iꞈ *et al.*, 2002; C s ꞈ iꞈs, 2003), t t it i ꞈ s ˀ ˀ ꞈiꞈ , ts st i st iꞈ i it t i sˀ st t ꞈ t ꞈ i t ꞈ st t . ꞈ t is st , it s iꞈ t t i t t ꞈ si t t i ˀs (50% t) ꞈ t s ssi s, t i sˀ ˀ ꞈ i ˀ st t i s (t iꞈ iꞈ isiti ꞈ ˀ ꞈiꞈ) s iꞈ i it .T s, t t's ꞈ iꞈ s ˀ ˀ ꞈ- iꞈ s i i iꞈt t s s: (i) t iꞈ i iti ꞈ s ꞈ (ii) t ꞈ -st t - isiti ꞈ s .

Clo apine adminis ra ion

Cˀ iꞈ (i -Aˀ i C t , t L is, U A) s isꞈ ˀ iꞈ ti i s ˀiꞈ s ˀ ti ꞈ, s H s st t ꞈ t ˀ it 10 ˀ/ˀ N H. C ꞈi iꞈist ti ꞈ ˀ iꞈ s ˀi iꞈ t ˀ s t stiꞈ t (6 8 s, ꞈ iꞈ ꞈ ꞈ). ꞈ t sis t ˀ iꞈ s s s iꞈ i s st i s (. . ˀ ꞈ G , 1993; is *et al.*, 2005; A ˀ- ꞈi *et al.*, 2006), iꞈ t is st t s ꞈ iꞈ i i ˀ t s 0, 5 10 / (it t ꞈst ꞈt iꞈ ti ꞈ ˀ 0.1 ˀ).T s, is ˀ ti ꞈ- ts ꞈ s i ˀˀ ts t . iꞈ t t s ˀ iꞈ . F t, t iꞈ ti ꞈ s iꞈist ꞈ i t iꞈt it ꞈ ˀ t 30 iꞈ ttiꞈ t t iꞈt t .

S a is ics

A ˀ t 2 (iꞈ t : s i ˀˀ iꞈ , is ˀ ti ꞈ iꞈ) 2 (is ˀ tt ꞈ ss isiti ꞈ ˀ ꞈiꞈ ꞈ s ˀ ˀ ꞈiꞈ : ˀi t/ , /ˀi t) 3 (ˀ iꞈ s : 0, 5, 10 /) t ꞈ- s si ꞈ s s iꞈ t is st . G ꞈ i ꞈ s t st siꞈ t - ꞈ ˀ s s i ꞈ (AN VAs). T ꞈ ˀ s s siꞈ 11.5 s t (C i , ˀˀiꞈ is, U A). i ꞈi i ꞈt ˀ ˀ s s t t 0.05. As 's t st is s t ꞈ ˀ ꞈꞈ is ꞈs ꞈ t ꞈs ꞈ is ꞈ t st st iꞈ ꞈt st- t sts, iꞈ t is st 's t st s s t ˀ ˀi iꞈ t s s si ꞈi i ꞈt ꞈ i ꞈ s.

Res l s

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

Aˀˀ t ts s iꞈ t is st t it i ꞈ is ˀ is i iꞈ ti ꞈ ˀ ꞈiꞈ , ꞈ t t ˀ t ti ꞈs t t t ˀ ꞈ t stiꞈ s ssi ꞈs t t it i ꞈ ss iꞈ i i ˀ ts. Fi 2 s s t ꞈ s t s ꞈs s t t it i ꞈ (ꞈ ˀ) ꞈ t ꞈ s s t t it i ꞈ (ꞈ ˀ).

F t t ꞈ t- s ꞈs t i ˀs ꞈ t ꞈ - s ꞈs t i ˀs t t it i ꞈ, AN VAs s t t ꞈ ꞈ t iꞈ ts iꞈt ti ꞈs ꞈ t t t s s si ꞈi i ꞈt ($P > 0.05$).

Re ersal learning

Aˀˀ t ts ꞈt ˀˀ t it i ꞈ s ˀ ˀ ꞈiꞈ , ꞈ t t s t i ti ꞈ iꞈ t ꞈ t stiꞈ s ssi ꞈs ss iꞈ i i ˀ ts. Fi 3 s s t ꞈ s t- s ꞈs t i ˀs t t it i ꞈ (ꞈ ˀ) ꞈ t ꞈ s - s ꞈs t i ˀs t t it i ꞈ (ꞈ ˀ). i sˀ, ts ꞈ t i ˀs t t ꞈ it i ꞈ iꞈ s ˀ ˀ ꞈiꞈ t ꞈ iꞈ i s isiti ꞈ ˀ ꞈiꞈ . ꞈ iti ꞈ, is ˀ ti ꞈ- ts t t it s ˀiꞈ iꞈ ti ꞈ ꞈ t i ˀs t t ˀ ꞈiꞈ it i ꞈ t ꞈ ꞈ t s s.

F t ꞈ t- s ꞈs t i ˀs t t it i ꞈ, t iꞈt ti ꞈ t ꞈ iꞈ t ꞈ ˀ iꞈ s

t i 's t t i s i t t .
t it i . isi , is ti - ts i t
it i t s 5 / si i i t
t t i 's t . t i it i t
s i ts i t it i (5 /)
$F(1,14) = 12.08$, $P < 0.001$. i . t
is ti - ts s i ts i t it
i t s 10 / , , s t
si i i t, $P > 0.05$.

t AN VAs 's s t t is ti -
ts, t s si i i t t i s
$F(2,21) = 123.14$, $P < 0.001$. 's st- t sts
s t t t t s si i i t
i t t . s 5 /
t i i t- i t t t s
10 / i is ti - ts (Fi . 3,).
t sti , s i ts, t s 's
si i i t t i s , $F(2,21) = 8.71$,
$P < 0.01$. 's st- t sts s t t t
0 / t 10 / si i i t
i t. 10 / t i st
t- s s t i 's t t it i
t t s 7(9.9s1-7( )26.6)-334(Fi . 3,s

(t)-8.4it i ,s

t - t -412.1-( )6373.9AN(V)-242.1(s s)-8.2
P si i i si s iit ti

As t i t ti t i t i
s s si i i t, t s t - AN VAs
. s s t t t s
si i i t i . t is ti - ts
s i ts i t it s 'i $F(1,14) = 246.73$,
$P < 0.001$, i i ti t t is ti - ts it t
i i ti si i i t t

F is ti - ts, 's st- t sts s
t t t t s s si i i t i t

is ti - ts i i i i ti
s i - ts (Fi . 4,). A 2 (i t)
3 (i s) AN VA s t t t i t ti
t t t t s s si i i t $F(2,42) = 83.85$,
$P < 0.001$ s t i t i t
$F(1,42) = 56.34$, $P < 0.001$ t i t
i s $F(2,42) = 42.96$, $P < 0.001$.

Disc ssion

As ati i at ti , i s st i s at at t t t is ti i s ai (*et al.*, 1962; s *et al.*, 1991; it s , 1996; , 2001; A - ai *et al.*, 2003; *et al.*, 2004), i i t t t t is ti i s ai as t at t t st. H , s i t at t s t t ti T s i t is st s si s t s t s iti ss i t it t i i t t sti i i t i i i t is ti i s ai .

Fi st, s ati i t s, t LED s t i t s i t t sti i t sti s ssi . s i at, ts t at t at is i ti t ' t' t t , it t i i at is is ti s. iti , s t sts i t i t t ti , t i t ti s, s s si at ts, t t st ts i t s i t sti s ssi . , i t sti s ssi , s s s s t st t , t t t , t t , s i i (ti) s i . Fi , s t t ti T t t i t siti s ti t i i , s i i - t s i .T , si t t ti T , ssi is ti ts at s t t i s t t sti t s, s s t s i i , is t , t iti T ( ) , s st ati .

T s ts t is st s .t t t it is ti i i i ti si ai i at ts isiti t si is is i i ti , is ti - ts, i t t i t it i , si ai i at t- s s t i t s i ts t t it i i s ai .T s i s s t t i s ts *et al.* (1962), s *et al.* (1991), i *et al.* (2004), i i ti t i i i t is ti i s ai .

t is st , , t t's is i i ti i i t s s it t t t - s s t i s, t t is ti i s ai s t si ai i at.T s, t s - at - si t t t t- s s t i s is s siti t s- ai i its t s at it t t t - s s t i s. t s at t t t t s siti it - s at si t - s s t i s is s i t st i t ss t ai it i . t ai

it i s st i at (s t it i s i t is st), s s ssi s t t it i ss i i ts, ti i - s i t t t s - s s t i s ss ts .

T ti i s - ai t s , ai s st i st s ss i s i i st t - i s t st is st t i s (i t s H t , 1969; s *et al.*, 1991; i *et al.*, 2002; C s i s, 2003).T s ts t is st i i t t t is ti - ts s s t si ai i at i i at i t i iti s (i i iti s) s ai , t i t t- s s t i s t i i it t i s i i st t . C ai i ist ti i , , i t t t is ti - i - i i i at i t i i iti s s ai . t -st t - isiti s . s ai , is ti - ts it t i i ti si ai i at t- s s t i s t t ai . it i t t is ti - ts it i i ti s i ts. T s, is ti i s t i i at s ai i t t i i iti s t -st t - isiti s s ai , t i t i i at i t -st t - isiti s .

ti si s t i i t i i t FC t si i i i at s ai i ts t st i t s T (L i , 1998). , i t st C s i s (2003), s ti si s t i i t FC s i i i i ts' i t - st t - isiti s s ai , s sti t t t i i t FC is i i ai t i s sti s ss i ti . ti si s t FC s i i i i ts' i t i i iti s s ai , s sti t t t FC is i i s ssi t i s sti - s ss i ti . T s ai i its s i t is st i t ss i t it s - ti s i t t FC t FC. ti , t s ts s i i s - ai i its i t -st t - isiti (t) s s st t t t i is ti - i -i t s- issi s, i s si t - i i i at i t t s s ai , ss i t it t FC.

t s t t is ti i s s i s s t t FC, i i ss (D - i's *et al.*, 2006), i s t i s t ai i siti s (L *et al.*, 2003, 2004),

[illegible]

[illegible]

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