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Dissociation between medial temporal lobe and basal ganglia memory systems in schizophrenia

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Abstract

The purpose of this study was to investigate basal ganglia (BG) and medial temporal lobe (MTL) dependent learning in patients with schizophrenia. Acquired equivalence is a phenomenon in which prior training to treat two stimuli as equivalent (if two stimuli are associated with the same response) increases generalization between them. The learning of stimulus–response pairs is related to the BG, whereas the MTL system participates in stimulus generalization. Forty-three patients with DSM-IV schizophrenia and 28 matched healthy controls participated. Volunteers received the Rutgers acquired equivalence task (face-fish task) by Myers et al. (2003) [Myers, C.E., Shohamy, D., Gluck, M.A. et al., 2003. Dissociating hippocampal versus basal ganglia contributions to learning and transfer. J. Cogn. Neurosci. 15, 185-193.], the California Verbal Learning Test (CVLT), and the *n*-back working memory test. The Rutgers acquired equivalence task investigates BG-dependent processes (stimulus–response learning) and MTL-dependent processes (stimulus generalization) with a single test. Results revealed that patients with schizophrenia showed a selective deficit on stimulus generalization, whereas stimulus–response learning was spared. The stimulus generalization deficit correlated with the CVLT performance (total scores from trials 1–5 and long-delay recall), but not with the *n*-back test performance. The number of errors during stimulus–response learning correlated with the daily chlorpromazine-equivalent dose of antipsychotics. In conclusion, this is the first study to show that patients with schizophrenia exhibit deficits during MTL-dependent learning, but not during BG-dependent learning within a single task. High-dose first generation antipsychotics may disrupt BG-dependent learning by blocking dopaminergic neurotransmission in the nigro-striatal system.
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1. Introduction

Memory dysfunction is one of the most consistently reported cognitive abnormalities in schizophre-

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nia. A quantitative review of 204 studies revealed that global verbal memory impairment was the most affected cognitive domain: 78% of patients with schizophrenia scored below the median of the joint control-patient aggregate sample (Heinrichs and Zakzanis, 1998). Another meta-analysis of 70 studies also concluded that the association between memory impairment and schizophrenia is robust and stable, with a special reference to the free recall of verbal material (Aleman et al., 1999). The neuropsychological pattern of memory deficit may be consistent with fronto-temporal pathology, although brain localization is still controversial (Cirillo and Seidman, 2003). A seminal functional neuroimaging study of memory retrieval showed impaired hippocampal recruitment but normal prefrontal activation in schizophrenia (Heckers et al., 1998). This finding can be interpreted as a circumscribed pathology of the hippocampus or an abnormal connectivity between the prefrontal cortex and the hippocampus. Reviewing data from structural and functional neuroimaging studies, Heckers (2002) concluded that regionally specific abnormality of the hippocampus and of memory functions is a core feature of schizophrenia.

The issue of memory impairment is further complicated by recent findings from humans and animals, revealing the existence of interacting and dissociable memory systems in the brain. The medial temporal lobe (MTL), including the hippocampus, has been associated with declarative (explicit) memory, which is important in the conscious acquisition and recollection of facts and events. In contrast, many non-declarative (implicit) memory functions, such as gradual learning of skills and habits, are linked to the basal ganglia (BG) (Schacter et al., 2000; Squire, 2004). The most widely used neuropsychological tests in schizophrenia research target the MTL declarative memory system, whereas the BG non-

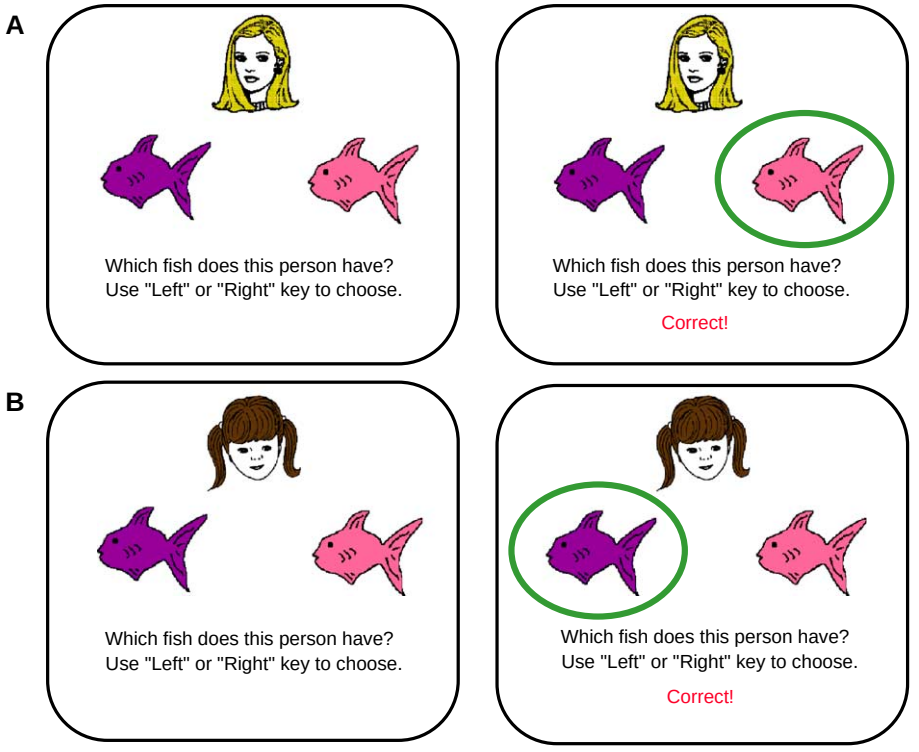

Fig. 1. The Rutgers acquired equivalence task. On each trial, the participant sees one face and two fishes (A). All three items appear at the same time. There is a prompt underneath instructing the participant to choose the left or right fish by pressing the correspondingly labeled key. The participant first has to make a random choice. The fish selected by the participant is then circled, and feedback appears ("Correct" or "Incorrect"). The feedback, together with the face, two fishes, and circle, remains on the screen for 1 s. The screen then goes blank for a 1 s inter-trial interval. Then the next trial is initiated, with a new face and new pair of fish appearing on the screen (B) (see also Table 1).

declarative memory system is less frequently investigated. The available data are controversial; whereas some studies indicated impaired skill and habit learning in schizophrenia (Schwartz et al., 1996, 2003), others provided evidence for intact BG-dependent learning (Kéri et al., 2000; Weickert et al., 2002). However, there is no published study that investigated BG- and MTL-dependent learning within the same task. This is an important issue because fundamental differences between the structure of the tests for declarative and non-declarative memory systems may result in false positive or negative findings. In this study, we used a single test, an acquired equivalence learning test, to demonstrate a dissociation between BG- and MTL-dependent learning in patients with schizophrenia. Another potential confounding factor is antipsychotic medication, which may disrupt dopaminergic neurotransmission in the nigro-striatal system and therefore may result in impaired skill and habit learning (Beninger et al., 2003).

The Rutgers acquired equivalence associative learning task (Myers et al., 2003) provides a unique opportunity to investigate BG- and MTL-dependent learning with a single task. This test is based on ample evidence from animal and clinical research, indicating that simple stimulus–response learning and flexible stimulus generalization are related to the BG and the MTL, respectively (Mishkin et al., 1984; Packard and Knowlton, 2002; Collie et al., 2002; Myers et al., 2002, 2003; Kéri, 2003). In the acquisition phase of the task, participants learn 6 pairs of stimulus–response associations. The stimuli are cartoons of persons' faces and color fishes and each person is associated with fishes with different colors (Fig. 1). Acquired equivalence is a phenomenon in which prior training to treat two stimuli as equivalent (if two stimuli are associated with the same response) increases generalization between them (Table 1). The learning of stimulus–response pairs is related to the BG, whereas the MTL system participates in acquired equivalence learning (Mishkin et al., 1984; Packard and Knowlton, 2002; Collie et al., 2002; Myers et al., 2002, 2003; Kéri, 2003).

The present study investigated the following issues: (i) BG- and MTL-dependent learning in patients with schizophrenia during the acquired equivalence associative learning task; (ii) the relationship between acquired equivalence learning and conventional measures of declarative memory (California Verbal Learning Test) and working memory (*n*-back task); (iii) the relationship between BG- and MTL-dependent phases of the acquired equivalence associative learning task and antipsychotic medication.

Table 1
The acquired equivalence paradigm

Acquisition stage 1: Shaping	Stage 2: Equivalence training	Stage 3: New consequences	Transfer phase: Equivalence testing
A1–X1	A1–X1	A1–X1	A2–X2?
	A2–X1	A2–X1	
		A1–X2	
B1–Y1	B1–Y1	B1–Y1	B2–Y2?
	B2–Y1	B2–Y1	
		B1–Y2	

During stage 1, participants learn the first 2 associations between different persons (A,B) and fishes (X,Y). During phase 2, different persons are associated with the same fishes (stimulus equivalence), whereas during stage 3, new consequences are added. During the transfer phase, participants are tested on the associations learned in stages 1–3 and also on new associations that are not learned during stages 1–3, but are the consequences of stimulus equivalence. This stimulus generalization phase is related to the medial temporal lobe, whereas learning during stages 1–3 is related to the basal ganglia (Myers et al., 2003).

2. Methods

2.1. Participants

Participants were 43 outpatients with schizophrenia (29 male, 14 female; paranoid ($n=12$), undifferentiated ($n=16$), residual ($n=11$), disorganized ($n=4$)) and 28 healthy control subjects (17 male, 11 female) with negative family history of schizophrenia-spectrum disorders and other psychoses (schizophrenia, schizophreniform disorder, schizoaffective disorder, brief psychotic disorder, bipolar disorder, and cluster A personality disorders). All patients lived in the community and 21 of them were employed at the time of testing (Table 2). The diagnosis was based on the DSM-IV criteria (American Psychiatric Association, 1994). All participants received the International Neuropsychiatric Interview Plus (Sheehan et al., 1998). Thirty-eight patients with schizophrenia received antipsychotic medications at the time of testing (haloperidol ($n=15$), zuclopenthixol ($n=5$),

Table 2
Clinical and demographical parameters

	Schizophrenia ($n=38$)	Control ($n=28$)
Age	38.6 (2.7)	37.5 (2.4)
Education	11.6 (2.4)	11.7 (3.0)
Duration of illness	12.5 (3.8)	–
PANSS P	13.1 (3.0)	–
PANSS N	12.4 (2.9)	–
PANSS G	28.3 (3.5)	–
CPZ	392.1 (47.9)	–

Data are mean (S.E.). PANSS—Positive and Negative Syndrome Scale, P—positive, N—negative, G—general symptoms; CPZ—chlorpromazine-equivalent dose of antipsychotics (mg/day).

chlorprothixene ($n=6$), fluphenazine ($n=4$), olanzapine ($n=3$), and risperidone ($n=5$)). Twelve patients received anticholinergic medication (biperiden). Five patients did not take antipsychotic medication because of the side effects (sedation and weight gain). They were outpatients and did not show acute psychotic symptoms. Clinical symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) (Table 2). History of neurological disorders, head injury, substance abuse, and electroconvulsive therapy were the exclusion criteria. After complete description of the study to the subjects, informed consent was obtained.

2.2. The Rutgers acquired equivalence task

Stimuli were presented and responses were collected using a Macintosh Power-Book laptop. The antecedent stimuli were four drawings of faces (man, woman, girl, boy). The consequents were drawings of fishes colored red, orange, purple, and pink. For each participant, faces and fishes were randomly assigned as antecedent and consequent stimuli. At the start of the experiment, the following instruction appeared on the screen: “Welcome to the experiment. You will see drawings of people who each have some pet fish. Different people have different kinds of fish. Your job is to learn which kinds of fish each person has. At first, you will have to guess.” The experimenter read the instruction aloud to the participant and then clicked the mouse button to begin the acquisition phase. On each trial, a face and two fish drawings were displayed on the computer screen along with the prompt: “Which fish does this person have? Use the Left or Right key to choose”. The participant responded with pressing one of two separate keys labeled as “LEFT” and “RIGHT” to indicate whether the fish on the left or the fish on the right was associated with the face. The selected fish drawing was circled and corrective feedback was given (Fig. 1). In the case of an incorrect response, an alert beep sounded. The left–right ordering of the fish drawings was randomized across subjects. There were three stages in the acquisition phase (Table 1). Stages 1 and 2 terminated after 8 consecutive correct responses, whereas stage 3 terminated after 12 consecutive correct responses. The participant was not informed on the beginning of a new stage. After the termination of the acquisition phase, a new instruction appeared on the screen, informing the participant that the task would remain the same but feedback would no longer be provided. The participant was not informed of the presence of new associations. The transfer phase consisted of 48 trials of which 12 trials were new associations for the testing of learned equivalence and 36 trials were old associations trained during the acquisition phase. The dependent measures were the mean number of errors in the acquisition phase and the proportion of incorrect responses in the transfer phase (for methodological details, see Myers et al., 2003).

2.3. IQ, declarative memory, and working memory

General intellectual functions were assessed with the revised version of the Wechsler Adult Intelligence Scale (WAIS-R) (Wechsler, 1981). Summary scores from trials 1–5 and long-delay recall scores of the CVLT were used to index declarative memory. The CVLT summary score was selected because this parameter was the most robust discriminating factor between schizophrenia patients and controls (Heinrichs and Zakzanis, 1998).

The *n*-back test, which was identical to that used by Callicott et al. (2000), was included to measure working memory. During this test, numbers between 1 and 4 were presented on the computer screen. In the 0-back condition, the participant was asked to detect the number and to press the corresponding button. In the 1-back condition, the participant viewed the first number and maintained that in the working memory. When the second number was viewed, the participant pressed the button that corresponded to the first num-

ber. In the 2-back condition, the participant recalled the number that had appeared "2 back" and pressed the corresponding button. The 0-back condition was a simple stimulus detection task, whereas in the 1-back and 2-back tasks there was an increasing demand on working memory to maintain the short-term representation of numbers (Callicott et al., 2000).

3. Results

Five patients with schizophrenia were unable to complete the acquisition phase. Three of them failed at stage 1 and 2 and 2 of them failed at stage 3. Four of them received high doses of first generation antipsychotics (mean: 1540.3 mg/day) and 1 patient failed to stay on task. The mean number of errors during the acquisition phase was 8.8 (S.E.=1.2) in the schizophrenia group and 7.7 (S.E.=1.8) in the control group. The difference was not statistically significant ($p=0.58$). In the transfer phase, the mean proportion of errors for old associations was 0.09 (S.E.=0.02) in the schizophrenia group and 0.08 (S.E.=0.02) in the control group. The mean proportion of errors for new associations was 0.41 (S.E.=0.04) in the schizophrenia group and 0.13 (S.E.=0.03) in the control group. An analysis of variance (ANOVA) conducted on the error rates for new and old associations in the transfer phase indicated significant main effects of group (patients vs. controls) ($F(1,64)=15.06$, $p<0.001$), type of associations (old vs. new) ($F(1,64)=59.73$, $p<0.0001$), and an interaction between group and type of associations ($F(1,64)=27.31$, $p<0.0001$). Planned comparisons with F-tests indicated that controls had similar error rates for new and old associations ($p=0.10$), whereas patients with schizophrenia performed much worse in the case of new associations ($F(1,64)=98.90$, $p<0.0001$). Tukey HSD post-hoc tests confirmed this robust dissociation, revealing that schizophrenia patients had more errors in the case of new associations ($p=0.0002$), but not in the case of old associations ($p=0.9$) as compared with the control group. These results remained unchanged when the patients receiving anticholinergic medication or second generation antipsychotics and the unmedicated patients were excluded from the analysis. Individual data revealed that 3 of the 28 controls (10.7%) scored below the median of the joint control-patient aggregate sample in the case of new association, whereas this rate was 27/38 (71.1%) in patients with schizophrenia.

Table 3 shows that patients with schizophrenia displayed impaired performances on the CVLT and n-back task. The n-back task scores did not correlate with dependent measures from the acquired equivalence task (Spearman's $R<0.3$). The CVLT scores showed a selective negative relationship with the error rate in the case of new associations during the transfer phase (summary score from trials 1–5: Pearson's $r=-0.66$, $p<0.05$; long-delay recall: Pearson's$=-0.64$, $p<0.05$). There was a positive relationship between the mean number of errors in the acquisition phase and the daily chlorpromazine-equivalent doses (Pearson's $r=0.76$, $p<0.05$) (Fig. 2). When the 4 outlier patients with very high daily dose of antipsychotics were excluded, the correlation remained significant (Pearson's $r=0.60$, $p<0.05$), similarly to the scenario when the 8 patients receiving second generation drugs were excluded (Pearson's $r=0.72$, $p<0.05$).

Table 3
IQ, CVLT, and n-back performances

	Schizophrenia ($n=38$)	Controls ($n=28$)
WAIS-R	102.3 (3.5)	104.8 (2.8)
CVLT trials 1–5	43.9 (1.4)[a]	53.9 (1.2)
CVLT long-delay recall	9.3 (0.5)[b]	11.3 (0.4)
0-back	10.0 (0.0)	10.0 (0.0)
1-back	7.7 (0.2)[c]	9.4 (0.1)
2-back	6.0 (0.3)[d]	8.3 (0.2)

Data are mean (S.E.). WAIS-R—Wechsler Adult Intelligence Scale, revised version; CVLT—California Verbal Learning Test; The CVLT scores were compared with two-tailed t-tests. The n-back scores were compared with Mann–Whitney U-test, because these values were not normally distributed.
[a] $t(64)=4.9$, $p<0.0001$.
[b] $t(64)=3.3$, $p<0.01$.
[c] $Z=4.8$, $p<0.0001$.
[d] $Z=5.3$, $p<0.0001$.

4. Discussion

The findings of this study indicate that patients with schizophrenia displaying preserved intellect (IQ) are impaired on tests of MTL-dependent learning, whereas BG-dependent learning is spared. This latter observation is consistent with the results of 2 previous studies, demonstrating intact BG-dependent cognitive skill learning in schizophrenia (Kéri et al., 2000; Weickert et al., 2002). A positive relationship was found between the daily dose of antipsychotics and errors during the acquisition phase, which suggests that antipsychotic medication disrupts BG-dependent learning, with a special reference to first generation antipsychotics with strong dopamine D2/D3 receptor inhibiting properties. These drugs, which were administered to the majority of the patients

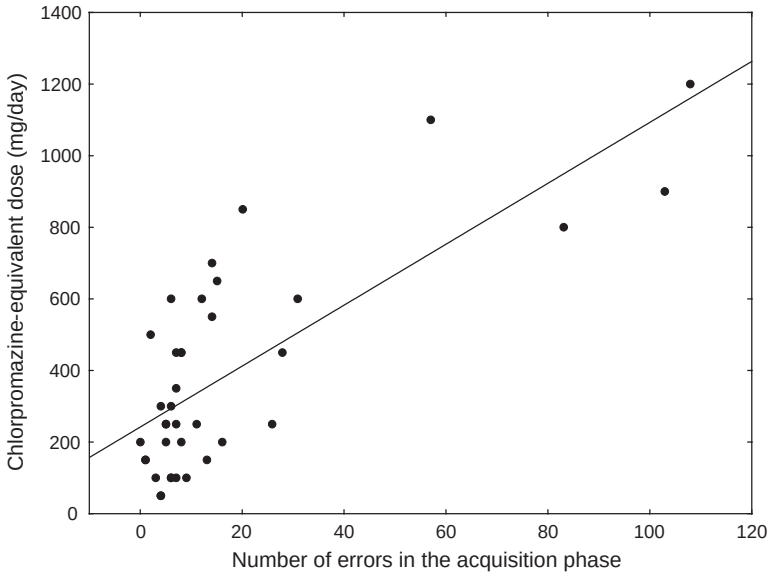

Fig. 2. Correlation between the daily chlorpromazine-equivalent antipsychotic dose and the number errors during the acquisition phase (Spearman's $r = 0.76$, $p < 0.05$).

participating in this study, may induce Parkinsonian symptoms by disrupting dopaminergic neurotransmission in the nigro-striatal system and may lead to impaired cognitive skill learning (Beninger et al., 2003). Indeed, in a prior study, patients with Parkinson's disease showed impaired stimulus–response learning during the acquisition phase, whereas transfer phase performance was spared (Myers et al., 2003). This is the opposite pattern to that found in patients with hippocampal atrophy who performed well during the acquisition phase, but had marked difficulties in the case of new associations during the transfer phase (Myers et al., 2003). Our sample of schizophrenia patients displayed an identical pattern of performance to that observed in patients with hippocampal atrophy. There was no significant between-group difference in the BG-dependent acquisition phase, probably because of the low dose of antipsychotics. However, the relationship between antipsychotic medication and errors in the stimulus–response learning phase suggests that higher doses of first generation antipsychotics would disrupt striatal learning during the acquired equivalence test. It is notable that 4 of the 5 patients who failed to complete the acquisition phase received very high doses of first generation antipsychotics and exhibited severe Parkinsonian symptoms.

The deficit observed in the transfer phase did not correlate with working memory impairments, suggesting that MTL-dependent functions are indeed impaired and memory dysfunction is not a mere consequence of prefrontal pathology. It has been suggested that the vast majority of memory dysfunctions in schizophrenia are due to encoding and recall abnormalities (Aleman et al., 1999; Cirillo and Seidman, 2003). Some authors suggested that a considerable proportion of schizophrenia patients show a so-called subcortical memory profile, which is characterized by impaired free recall and relatively preserved recognition (Paulsen et al., 1995; Turetsky et al., 2002). However, the subcortical profile in schizophrenia was found to be inconsistent across ability areas, and is not likely to be the result of stable structural or functional brain deficits in the fronto-striatal system (Harvey et al., 2002). In our study, subcortical memory functions did not show a robust impairment in contrast to hippocampal stimulus generalization, which is against a general and severe BG pathology in schizophrenia. The impaired recall of words in the CVLT correlated with the acquired equivalence deficit, which supports the view that CVLT impairments are related to MTL pathology in schizophrenia. Heckers et al. (1999) demonstrated that during word recall, impaired hippocampal recruitment was a common feature in all

types of schizophrenia, whereas abnormal frontal activation was observed only in schizophrenia patients with enduring negative symptoms (deficit syndrome). It is notable that acquired equivalence does not include declarative memory formation and retrieval in the conventional sense, that is, this task requires neither conscious encoding nor conscious recall of facts and events. Instead, acquired equivalence is based on stimulus generalization between items that are associated with the same response (Myers et al., 2003). This flexible generalization of previously learned stimulus–response associations is related to the MTL, which is severely affected in patients with schizophrenia.

It should be taken into consideration that the differential deficit between BG- and MTL-dependent learning may be a psychometric artifact, because increased difficulty and higher performance variance may produce differences between schizophrenia patients and healthy controls (Chapman and Chapman, 1978; Miller et al., 1995). There are several facts that argue against the possibility that the differential acquired equivalence impairment is a psychometric artifact. First, healthy controls did not achieve significantly more errors in the case of new associations than in the case of old associations during the transfer phase, although the error rate was numerically higher in the case of new associations. This suggests that new associations were not more demanding than old associations. Second, true-score variance (a product of task reliability and task variance) was 0.006 in the case of new associations and 0.02 in the case of old associations. It is assumed that schizophrenia patients show a generalized cognitive dysfunction and a greater performance deficit on tasks with greater true-score variance (Miller et al., 1995). In our case, a selective deficit was found for the task component with a smaller true-score variance (new associations during the transfer phase), which is against the possibility that our finding is a psychometric artifact. Third, a previous study demonstrated a double dissociation between stimulus–response learning and acquired equivalence, which supports the view that these subcomponents of the task are mediated by different brain systems (Myers et al., 2003). Fourth, the robust difference between patients and controls can hardly be explained exclusively by the psychometric properties of the task.

To our knowledge, this is the first study to demonstrate dissociation between different memory systems in patients with schizophrenia within a single task. The acquired equivalence associative learning task is a unique procedure with which genetic aspects of cognitive impairments and medication effects on different memory systems can be investigated.

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