Associative learning in deficit and nondeficit schizophrenia

Márta Farkas[a], Patricia Polgár[a], Oguz Kelemen[b], János Réthelyi[a], István Bitter[a], Catherine E. Myers[c], Mark A. Gluck[d] and Szabolcs Kéri[a]

[a]Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, [b]Bács-Kiskun Country Hospital, Psychiatry Unit, Kecskemét, Hungary, [c]Department of Psychology and [d]Center for Neuroscience, Rutgers University, Newark, New York, USA

Correspondence to Dr Szabolcs Kéri, Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest HI083, Balassa u. 6., Hungary
Tel: + 36 20 448 3530; e-mail: szkeri@phys.szote.u-szeged.hu

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When two stimuli are associated and treated as equivalent, generalization occurs between them (acquired equivalence). The feedback-guided learning of associations is related to the basal ganglia, whereas the medial temporal lobe participates in acquired equivalence learning. In this study, we investigated feedback-guided associative learning and acquired equivalence in deficit and nondeficit schizophrenia. Results revealed that acquired equivalence learning was similarly impaired in deficit and nondeficit patients, whereas feedback-guided associative learning was impaired only in deficit patients. Associative learning and acquired equivalence were not related to frontal lobe tests. These results suggest that the enduring negative symptoms of deficit patients may be related to decreased response to cognitive feedback and deficient basal ganglia functioning. *NeuroReport* 19:55–58 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Learning associations between stimuli and generalization of such associations are essential for everyday cognition. For example, one may use feedback to learn that John is a fan of soccer teams Manchester United and Green Eagles and that Peter also likes Manchester. On the basis of these associations, one may infer that John and Peter have similar preferences for soccer teams, and therefore Peter also likes Green Eagles. This phenomenon is called acquired equivalence. Previous studies in animals and humans raised the possibility that the basal ganglia are essential to use feedback in the learning of associations, whereas the medial temporal lobe, including the hippocampus, is indispensable for acquired equivalence learning [1–3].

Schizophrenia, a heterogeneous and severe mental disorder with symptoms of hallucinations, delusions, flattened affect, and social impairment, is characterized by marked memory dysfunctions, which are mainly related to the medial temporal lobe [4]. One of the most valid and widespread classifications of this amazingly complex illness focuses on the concept of deficit and nondeficit subtypes [5–7]. Deficit patients are characterized by enduring negative symptoms, including flattened affect, anhedonia, poverty of speech, curbing of interest, lack of sense of purpose, and decreased social drive. These symptoms are not accounted for by depression, anxiety, medication side effect, hallucinations, delusions, or psychosocial deprivation [5].

Despite the intensive investigation of deficit and nondeficit schizophrenia, features of associative learning are not known in these subtypes. In this study, we used an acquired equivalence test to investigate basal ganglia-dependent, feedback-guided associative learning, and medial temporal lobe-dependent acquired equivalence learning in deficit and nondeficit schizophrenia. Our hypothesis was that deficit patients are less able to use feedback and they show more severe impairment during the learning of associations compared with nondeficit patients. We also administered a brief battery of classic neuropsychological tests sensitive for frontal lobe functioning to investigate the potential contribution of this brain region to associative learning.

Methods

Participants

The patients were recruited at the Bács-Kiskun County Hospital and at the Semmelweis University, Department of Psychiatry and Psychotherapy. The healthy control volunteers were employees of these institutions and their acquaintances. The diagnosis was based on the criteria of the *Diagnosis and Statistical Manual of Mental Disorders-IV* [8]. All participants received the Mini-International Neuropsychiatric Interview [9]. The deficit syndrome was assessed using the Schedule for the Deficit Syndrome [10]. Clinical symptoms were evaluated with the Positive and Negative Syndrome Scale [11]. The two subgroups of patients were matched for age, sex, education, duration of illness, positive and general symptoms, and type and chlorpromazine-equivalent dose of antipsychotic medications (Table 1). The study was done in accordance with the Declaration of Helsinki and was officially approved.

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Acquired equivalence test

The computer-based acquired equivalence task studied by Myers *et al.* [3] has been described in details elsewhere. Stimuli were presented 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 instructions 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.' 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).

After the feedback-guided training 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 acquired equivalence and 36 trials were old associations learned during the training phase. For example, the participant learned during the training phase that the man had red and orange fish and the girl had red fish. These are old associations that were presented and tested during the transfer phase. In addition, the participant faced the question of whether the girl had orange fish or not. This is a new association that can be formed according to the principle of acquired equivalence. The dependent measures were the mean number of errors in the training phase and the proportion of incorrect responses in the transfer phase.

Table 1 Demographic characteristics and neuropsychological results

	Controls	Nondeficit	Deficit
N	20	26	23
Male/female	14/6	18/8	15/8
Age (years)	35.4 (7.5)	36.1 (9.6)	37.1 (10.0)
Education (years)	10.9 (3.8)	10.6 (7.3)	10.1 (5.6)
Duration of illness (years)	—	12.0 (5.1)	13.4 (6.2)
Type of antipsychotic medication (second-generation/first-generation/both)	—	20/3/3	19/4/0
Chlorpromazine-equivalent dose of antipsychotics (mg/day)	—	375.6 (192.7)	360.0 (194.5)
PANSS-P	—	13.1 (5.2)	14.9 (6.9)
PANSS-N	—	15.4 (5.4)	24.4 (3.4)
PANSS-G	—	36.0 (14.0)	36.5 (11.2)
WCST[a]	9.9 (6.0)	14.9 (3.6)	23.3 (14.0)
TMB[b]	55.6 (19.3)	90.0 (27.5)	113.6 (46.8)
COWAT[c]	39.4 (10.7)	28.4 (12.1)	22.1 (12.6)
AET – errors in the training phase[d]	7.2 (9.1)	9.0 (15.6)	22.5 (23.4)
AET – proportion of errors, old associations[e]	0.12 (0.15)	0.08 (0.11)	0.11 (0.11)
AET – proportion of errors, new associations[f]	0.17 (0.22)	0.39 (0.27)	0.37 (0.24)

Data are mean (standard deviation). AET, Acquired Equivalence Test; COWAT, Controlled Oral Word Association Test, number of retrieved words; G, general symptoms; N, negative symptoms; P, positive symptoms; PANSS, Positive and Negative Syndrome Scale; TMB, Trail Making B, time to complete; WCST, Wisconsin Card Sorting Test, number of perseverative errors.

[a]One-way ANOVA: $F(2,66)=9.60$, $P<0.001$; deficit > nondeficit=controls (Scheffé: $P<0.05$).

[b]One-way ANOVA: $F(2,66)=16.11$, $P<0.001$; deficit > nondeficit > controls (Scheffé: $P<0.05$).

[c]One-way ANOVA: $F(2,66)=10.87$, $P<0.001$; controls > deficit=nondeficit (Scheffé: $P<0.05$).

[d]Deficit > nondeficit=controls.

[e]No significant differences.

[f]Nondeficit=deficit > controls (for the details of statistical analysis, see the text).

Background neuropsychology

Classic tests sensitive for frontal lobe functioning were administered as described previously [7,13]. In the Wisconsin Card Sorting Test, participants were asked to sort cards according to the color, form, and number of geometric shapes. After the learning of correct strategy, the rule was changed (e.g., cards must have been categorized according to form and not color). Inability to shift the strategy (perseveration) is a sign of frontal lobe impairment. In the Trail Making B tests, participants were asked to connect numbers and letters in an alternating sequence (1-A-2-B-3-C and so on), and the time necessary for the completion of the procedure was measured. In the Controlled Oral Word Association Test, participants were asked to retrieve as many words beginning with letter F, A, and S as they could during a 1-min period.

Statistical analysis

Repeated measures analysis of variance (ANOVA) was used with group (controls, deficit, and nondeficit patients) as the between-subject factor and with dependent measures of tests as the within-subject factor. Scheffé's tests were used for post-hoc analysis. Pearson's correlation coefficients were calculated between clinical measures and test results. The level of significance was $\alpha<0.05$.

Results

Acquired equivalence test

The ANOVA conducted on the mean number of errors in the training phase revealed a significant main effect of group [$F(2,66)=9.6$, $P<0.01$]. Scheffé's tests indicated no significant difference between nondeficit patients and controls ($P>0.2$). In contrast, deficit patients committed more errors than controls ($P<0.001$) and nondeficit patients ($P<0.01$) (Table 1).

The ANOVA conducted on the mean proportion of errors in the testing (transfer) phase revealed significant main effects of group [$F(2,66)=3.32$, $P<0.05$] and association type (old vs. new associations) [$F(1,66)=40.28$, $P<0.001$]. The two-way interaction between group and association type was significant [$F(2,66)=5.16$, $P<0.05$]. Scheffé's tests revealed that both deficit and nondeficit patients showed more errors in the case of new association compared with controls ($P<0.05$). Such differences, however, were not found in the case of old associations ($P>0.5$), and deficit and nondeficit patients did not differ ($P>0.5$) (Table 1).

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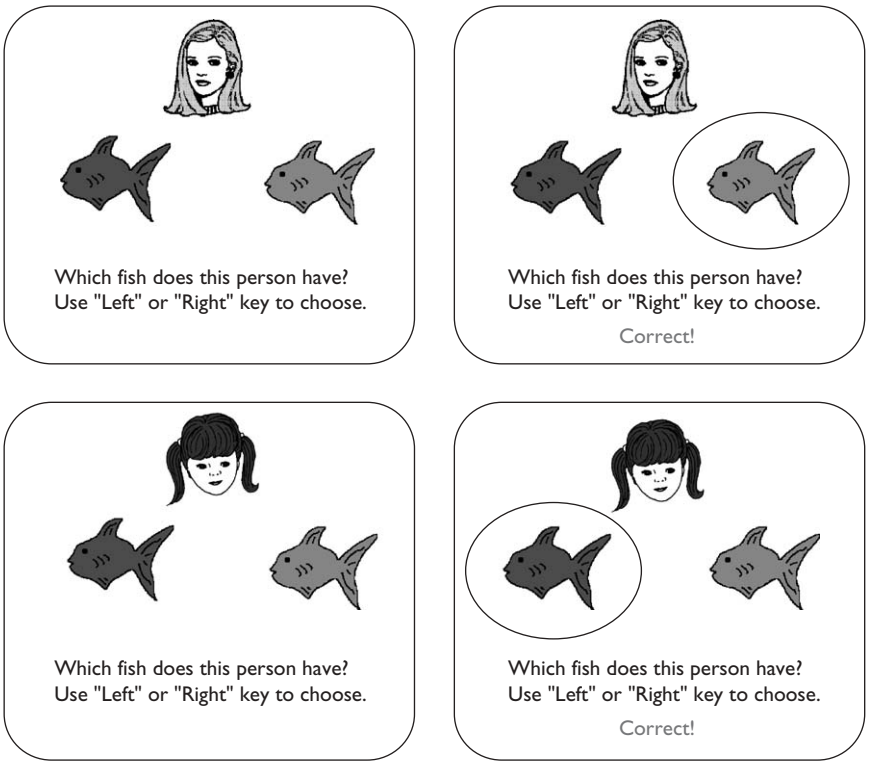

Fig. 1 Example of an experimental trial. First, stimuli appeared on the screen. The participant then responded, the chosen fish was circled, and corrective feedback was given.

Background neuropsychology

The results are shown in Table 1. In general, patients with schizophrenia were impaired on each frontal test, and nondeficit patients outperformed deficit patients. This pattern, however, varied in the case of three different tests (Table 1).

Correlations

A significant positive relationship between the number of errors in the training phase of the acquired equivalence test and negative symptoms (r=0.51, $P<0.05$) was found. No significant correlation between acquired equivalence test scores and antipsychotic dose ($P>0.2$) was found. Finally, there was no significant relationship between frontal lobe and acquired equivalence test scores ($P>0.2$).

Discussion

This study lends support for the assumption that deficit schizophrenia cannot be conceptualized simply as a syndrome with more severe generalized cognitive dysfunctions. Crucially, deficit and nondeficit patients showed similar acquired equivalence learning, which was less efficient than that seen in controls [12]. This is against the possibility of a generalized cognitive impairment in deficit patients, which may affect each phase of the task. Deficit patients committed more errors in the feedback-guided training phase than controls, which was not characteristic for nondeficit patients. This is consistent with the observation that patients with schizophrenia are able to learn simple associations but are markedly impaired when these associations must be used for new inferences (as in the case of acquired equivalence), put in new context [7], or when associations must be flexibly modified [14].

The higher error rate of deficit patients in the feedback-guided training phase and the selective correlation between negative symptoms and errors suggest that the deficit syndrome may be associated with a blunted response to cognitive feedback [7,15]. Evidence indicates that the striatal region is important in the processing of such cognitive feedback [16], and that this region is underresponsive in schizophrenia patients with negative symptoms [17].

The lack of any correlation between acquired equivalence test scores and frontal lobe test results may indicate that simple associative learning and acquired equivalence do not depend on higher-level executive functions, similarly to other cognitive skills based on stimulus–response learning [7,18,19]. In this respect, it is notable that acquired equivalence learning is severely impaired in patients with medial temporal lobe atrophy [3], raising the possibility that this brain structure is especially important in the generation of new associations. This medial temporal lobe function was impaired in both deficit and nondeficit schizophrenia. The degree of impairment in the medial temporal lobe-dependent transfer phase was similar in both deficit and nondeficit patients, which is against the possibility that deficit patients perform more poorly than nondeficit patients on each aspect of cognitive tests (generalized cognitive impairment).

Previous studies revealed that first-generation (typical) antipsychotic drugs, which strongly block dopamine receptors in the striatum, impair even basic associative learning [12,20]. In this study, however, the majority of patients

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received second-generation (atypical) antipsychotics with weaker dopamine receptor affinity. This can explain the lack of correlation between antipsychotic dose and errors in the training phase of the acquired equivalence test.

Conclusions

The results of the present study lend further support for the dissociation between feedback-guided learning of association and forming new association on the basis of previous information (acquired equivalence). The former is mediated by the basal ganglia, whereas the latter is related to the medial temporal lobe. This dissociation may be helpful in the definition of the cognitive characteristics of deficit and nondeficit schizophrenia.

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