

How to find the way out from four rooms? The learning of “chaining” associations may shed light on the neuropsychology of the deficit syndrome of schizophrenia

Patricia Polgár^a, Márta Farkas^a, Orsolya Nagy^b, Oguz Kelemen^b, János Réthelyi^a,
István Bitter^a, Catherine E. Myers^c, Mark A. Gluck^d, Szabolcs Kéri^{a,*}

^a *Semmelweis University, Department of Psychiatry and Psychotherapy, Budapest, H1083, Balassa u. 6., Hungary*

^b *Bács-Kiskun Country Hospital, Psychiatry Unit, Kecskemét, Hungary*

^c *Department of Psychology, Rutgers University, Newark, NY, USA*

^d *Center for Neuroscience, Rutgers University, Newark, NY, USA*

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Abstract

Recent meta-analytic evidence suggests that clinical neuropsychological methods are not likely to uncover circumscribed cognitive impairments in the deficit syndrome of schizophrenia. To overcome this issue, we adapted a cognitive neuroscience perspective and used a new “chaining” habit learning task. Participants were requested to navigate a cartoon character through a sequence of 4 rooms by learning to choose the open door from 3 colored doors in each room. The aim of the game was to learn the full sequence of rooms until the character reached the outside. In the training phase, each stimulus leading to reward (open door in each room) was trained via feedback until the complete sequence was learned. In the probe phase, the context of rewarded stimuli was manipulated: in a given room, in addition to the correct door of that room, there also appeared a door which was open in another room. Whereas the training phase is dominantly related to basal ganglia circuits, the context-dependent probe phase requires intact medial-temporal lobe functioning. Results revealed that deficit and non-deficit patients were similarly impaired on the probe phase compared with controls. However, the training phase was only compromised in deficit patients. More severe negative symptoms were associated with more errors on the training phase. Executive functions were unrelated to performance on the “chaining” task. These results indicate that the deficit syndrome is associated with prominently impaired stimulus–response reinforcement learning, which may indicate abnormal functioning of basal ganglia circuits.

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1. Introduction

The heterogeneity of patients is one of the most fundamental problems in schizophrenia research. A particularly important milestone in the field was the introduction

of the concept of the deficit syndrome. According to [Carpenter and Kirkpatrick \(1988\)](#), schizophrenia patients with deficit syndrome 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, positive symptoms or psychosocial deprivation.

* Corresponding author. Tel.: +36 20 448 3530.

E-mail address: szkeri@phys.szote.u-szeged.hu (S. Kéri).

Although the construct validity of the deficit syndrome has been supported by various clinical, epidemiological, and biological findings (Kirkpatrick et al., 2001), a clear neurocognitive profile of the syndrome is still missing. Originally, Buchanan et al. (1994) proposed that frontal and parietal functions are especially impaired in deficit patients, but data from some subsequent studies failed to support this hypothesis (e.g. Brazo et al., 2002; Galderisi et al., 2002; Seckinger et al., 2004; Tiryaki et al., 2003). In a meta-analysis of 13 studies, Cohen et al. (2006) found that deficit patients were globally more neuropsychologically impaired than non-deficit patients, with the largest differences in olfaction and social cognition. Therefore, more precise cognitive neuroscience methods are warranted to find potentially specific differences between deficit and non-deficit patients.

To achieve this aim, we used a “chaining” association task originally developed by Shohamy et al. (2005) and Nagy et al. (2007a). The task is motivated by evidence suggesting that the medial temporal lobe (MTL) and the basal ganglia (BG) play distinct roles in learning and memory. The MTL, including the hippocampus, is important in declarative memory functions, whereas the BG is essential for learning habits and skills, such as associations between stimuli and responses (Squire et al., 2004; Yin and Knowlton, 2006). The gradual learning of cognitive habits and skills requires the processing of

feedback and reinforcement following decisions and responses. Although the MTL may not be necessary for such reinforcement-based stimulus–response learning, it is important in more complex situations when familiar stimuli are presented in a novel context (Manns and Eichenbaum, 2006). For example, one can easily learn that pressing a blue switch leads to the turning on of the air conditioner in the bedroom (trial-by-error stimulus–response learning based on feedback). However, it is possible that in the kitchen (novel context) the blue switch has a different role. In this case, the non-flexible stimulus–response habit may lead to erroneous consequences, and the context must be taken into consideration for a successful behavior.

In patients with Parkinson’s disease, Shohamy et al. (2005) and Nagy et al. (2007a) demonstrated that the BG are involved in the learning of sequential (“chaining”) stimulus–response associations, in which each link in a sequence of stimuli leading to reward is trained step-by-step using feedback after each partial sequence is executed, until the complete sequence is learned. During the “chaining” task, participants were required to learn a sequence of events leading to reward. In the first phase of this task, the computer screen showed a room (room 1) with 3 doors (A, X, Y), each bearing a colored card; the participant was required to choose one of these doors by guiding a cartoon character (Fig. 1). Choosing the open

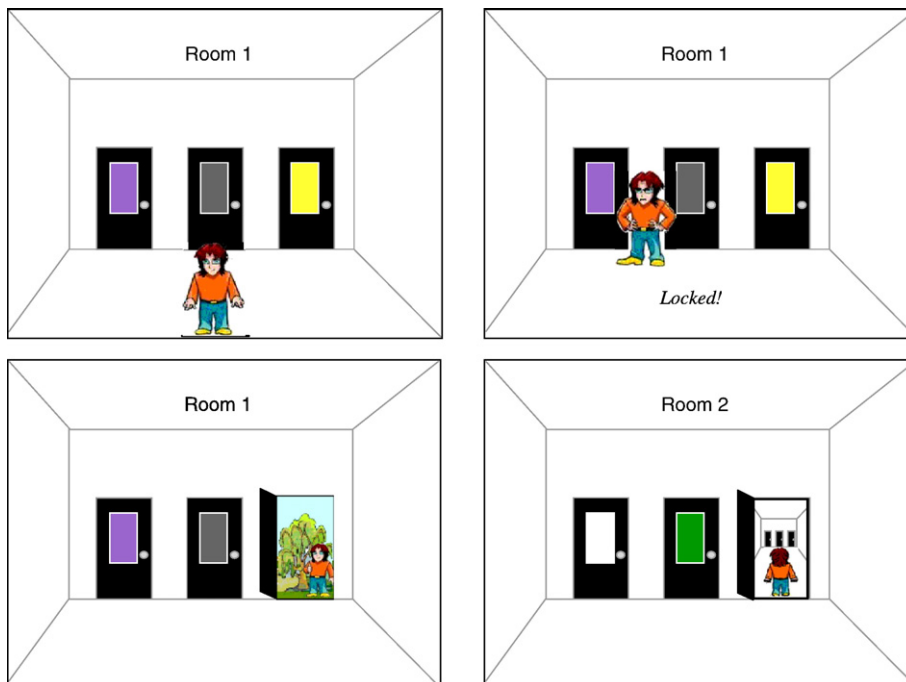


Fig. 1. Display of the “chaining” task. Upper row: The participants chose the closed door in room 1. Lower row, left panel: The participant chose the open door in room 1 and Kilroy reached outside. Lower row, right panel: In room 2, the participant chose the open door and Kilroy entered into room 1.

door (for example, door A) led to a garden (reward), while an incorrect response (X or Y) did not, and the participant had to try again. Once this A→reward association was learned, the participant was presented with another room (room 2) with 3 new colored doors (B, W, Z). An incorrect response (W or Z) led to a closed door, while a correct response (door B) led to room 1, where the participant would again choose the correct door (A) to reach the reward. Once this new association (B→A→reward) was learned, a new room was added to the sequence, until eventually the participant learned a full sequence: D→C→B→A→reward. Shohamy et al. (2005) and Nagy et al. (2007a) found that unmedicated Parkinson's disease patients were normal at learning simple, one-step associations (e.g., A→reward), but increasingly impaired at further learning as the length of the chain increased.

The task also contained a probe phase, which was designed to test stimulus–response habits in novel contexts. After the learning of the chain of associations, the colors of the incorrect doors were switched such that in each room, in addition to the correct door for that room, there also appeared a door which was the correct door elsewhere in the sequence. Thus, for example, in room 2, the participant might be presented with a choice between door B (correct), A (incorrect at this point in the sequence but correct in another room), and X (never correct). The probe phase was designed to verify that the participant had learned the correct door in its correct place in the sequence (learning in a sequential manner). A participant who had learned the sequence should always make the correct response (choose door B in room 2), regardless of what other doors are present. But if the participant learned the correct door but had no knowledge of its place in the sequence (an absence of contextual knowledge), then in room 2, he or she might have mistakenly choose door A, which had also been associated with reward. Among those unmedicated Parkinson's disease patients who were able to learn the full, four-step chain, Shohamy et al. (2005) and Nagy et al. (2007a) found probe phase performance that was not significantly different from controls. Interestingly, patients with amnesic mild cognitive impairment with MTL pathology showed intact learning during the stimulus–response training phase, but their performance was impaired in the contextual probe phase, exactly the opposite to that found in Parkinson's disease (Nagy et al., 2007a). These results indicate that compromised BG functions result in less efficient stimulus–response learning, but the sequential manner of associations is maintained. In contrast, MTL dysfunctions may result in a non-sequential learning of associations, which may indicate a loss of contextual information.

The aim of this study was to explore whether deficit patients show a generalized cognitive impairment or whether some functions are less severely affected. If there is a generalized impairment, as we hypothesized based on the meta-analysis of Cohen et al. (2006), deficit patients should show more errors during both the training and probe phases of the “chaining” task compared with non-deficit patients. Finally, we administered neuropsychological tests sensitive for frontal lobe functioning (Strauss et al., 2006) in order to investigate the relationship between “chaining” task performance and executive functions. Based on previous data from studies investigating habit learning and executive functions (Kéri et al., 2005a; Waltz et al., 2007; Weickert et al., 2002), we expected to find no relationship between frontal lobe tests and “chaining” task performance.

2. Methods

2.1. Participants

Participants were 78 patients with schizophrenia and 30 healthy control volunteers with negative psychiatric history (Table 1). The patients were recruited at the Bács-Kiskun County Hospital and at the Semmelweis University, Department of Psychiatry and Psychotherapy. The control volunteers were employees of these institutions and their acquaintances, who were matched with the patients for age, gender, and education. The diagnosis was based on the DSM-IV criteria (American Psychiatric Association, 1994). All participants, including the controls, received the International Neuropsychiatric Interview Plus (Balázs et al., 1998; Sheehan et al., 1998). With the exception of three cases, all patients received antipsychotic medications (Table 1). People with alcohol and drug abuse did not participate in the study. The deficit syndrome was assessed using the Schedule for the Deficit Syndrome (SDS) (Kirkpatrick et al., 1989). The deficit status of the patients was evaluated with a standardized interview and was based on an agreement between an independent assessor and the treating clinician ($\kappa=0.78$). Clinical symptoms were evaluated with the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987) (Table 1). After complete description of the study to the subjects, written informed consent was obtained.

2.2. The “chaining” task

The procedure has been described in details elsewhere (Kéri et al., 2007; Nagy et al., 2007a,b) and has also been explained in the introduction. The task was

Table 1
Demographic and clinical characteristics of the participants

	Controls	Non-deficit	Deficit
<i>N</i>	30	45	27
Male/female	20/10	32/13	22/5
Age	38.3 (8.9)	35.1 (10.6)	37.9 (9.0)
Education	11.4 (3.5)	11.6 (6.3)	10.4 (7.4)
Duration of illness	–	13.3 (6.0)	14.5 (7.1)
Type of antipsychotic medication (second generation/first generation/both) ⁺	–	39/3/1 (2 unmedicated)	25/1/0 (1 unmedicated)
Chlorpromazine-equivalent dose (mg/day)	–	368.5 (182.3)	342.0 (174.8)
PANSS P	–	14.1 (6.7)	13.5 (5.3)
PANSS N	–	17.2 (8.2)	23.5 (7.0)*
PANSS G	–	35.1 (11.6)	39.1 (14.5)

Data are mean (standard deviation). PANSS — Positive and Negative Syndrome Scale, P — positive, N — negative, G — global. * $t(64)=3.35, p=0.001$.
⁺The patients received second-generation drugs at least for 16 weeks before testing, and there were no clinically relevant extrapyramidal symptoms. Twenty-two non-deficit and 14 deficit patients received first-generation drugs during their previous treatment.

run on a Macintosh OS9 computer. On each trial of the experiment, the animated character (nicknamed Kilroy) appeared in a room with three doors with different colors (Fig. 1). The participant used the computer mouse to move the cursor to click on one of the doors. Kilroy walked to the door, and tried to open it. If the participant's choice was incorrect, the door was "locked" and Kilroy could not open it. If the participant's choice was correct, Kilroy opened the door and stepped through. In each room, the same three colored cards always appeared, but spatial location of the cards was shuffled across trials.

A trial consisted of a full sequence of rooms until Kilroy reached the outside. The length of this sequence increased from 1 to 4 rooms over the course of training. Each sequence learning trial continued until the participant completed 4 consecutive correct trials or to a maximum of 15 trials. If the participant was not able to learn during the 15 trials, the task was terminated.

After the learning of the sequence of four associations, the probe phase began, un signaled to the participant. In this phase, in each room, 1 of the 3 colored doors was correct in the current room; 1 was correct in a different room, that is, at a different point of the sequence, and 1 was never correct in any room. The probe phase contained 6 trials, each trial consisting of a trip through the usual 4 rooms. Finally came a retraining phase, in which the participant was required to learn a new room with 3 new colored doors, one of which led directly to the outside. The purpose of this phase was to determine whether any learning deficits observed on the probe phase were due to fatigue effects.

2.3. Neuropsychological assessment

We used 3 widely applied neuropsychological tests to measure frontal lobe functioning. These included

FAS fluency (total number of words recalled), Wisconsin Card Sorting Test (WCST) number of perseverative errors, and Trail Making B time to completion (Strauss et al., 2006).

2.4. Data analysis

The STATISTICA 6.0 package was used for data analysis (StatSoft, inc., Tulsa). First, data were entered into Kolmogorov–Smirnov tests in order to check the normality of distribution. Since data showed normal distribution, analyses of variance (ANOVAs) were used, followed by two-tailed *t*-tests. Pearson's correlation coefficients (*r*) and linear regressions were used to assess the relationship between relevant variables. The level of significance was set at $\alpha < 0.05$.

3. Results

3.1. Neuropsychological assessment

Table 2 shows that patients with schizophrenia were impaired on all tests of frontal lobe functioning as compared with controls. In addition, patients with deficit syndrome performed worse than non-deficit patients.

3.2. The "chaining" task

From the 78 patients, 6 patients were not able to complete the "chaining" task. These patients were excluded from the analysis. In the control group, all participants were able to complete the task.

In the first ANOVA, the between-subject factor was the group (controls, deficit and non-deficit patients) and the within subject factor was the number of errors in the training phase (collapsed across the 4 phases) and in the

Table 2
Neuropsychological results

	Controls	Non-deficit	Deficit	<i>F</i> (<i>df</i>)	<i>t</i> (<i>df</i>)	<i>t</i> (<i>df</i>)	<i>t</i> (<i>df</i>)
	(C) (<i>n</i> =30)	(ND) (<i>n</i> =45)	(D) (<i>n</i> =27)	<i>p</i>	<i>p</i>	<i>p</i>	<i>p</i>
					C vs. ND	C vs. D	D vs. ND
WCST	9.9 (5.7)	17.0 (10.5)	23.7 (13.9)	12.33 (1.99) <0.0001	−3.35 (73) 0.001	−4.98 (55) <0.0001	−2.31 (70) 0.02
FAS	40.1 (10.3)	30.7 (12.8)	22.2 (13.6)	15.05 (1.99) <0.0001	3.34 (73) 0.001	5.65 (55) <0.0001	2.68 (70) 0.01
TMB	58.0 (22.0)	91.2 (38.2)	112.9 (48.6)	17.81 (1.99) <0.0001	−4.86 (73) <0.0001	−5.60 (55) <0.0001	−2.26 (70) 0.03

Data are mean (standard deviation). WCST — Wisconsin Card Sorting Test number of perseverative errors, FAS — FAS fluency number of recalled words, TMB — Trail Making B time to complete. *F*-values are from one-way ANOVAs.

probe phase, as shown in Table 3. This ANOVA revealed significant main effects of group ($F(2,99)=11.21$, $p<0.001$), errors ($F(1,99)=22.18$), and a significant two-way interaction ($F(2,99)=5.62$, $p<0.05$). The two-way interaction remained significant when controls were contrasted with non-deficit patients ($F(1,99)=11.21$, $p<0.01$), but not when controls were contrasted with deficit patients ($p=0.1$). Non-deficit patients displayed significantly more errors than controls on the probe phase ($t(73)=-3.70$, $p<0.001$), but not on the training phase ($p>0.1$). Deficit patients were less accurate than controls on both the probe ($t(55)=-4.96$, $p<0.001$) and training phases ($t(55)=-4.71$, $p<0.001$). Critically, deficit and non-deficit patients displayed statistically similar performance on the probe phase ($p>0.1$), whereas deficit patients committed more errors on the training phase than did non-deficit patients ($t(70)=-3.01$, $p<0.01$) (Table 3).

In the second ANOVA, we explored the differences between the groups in the 4 training phases of the task (from 1 to 4 rooms). This ANOVA indicated significant main effects of group ($F(2,99)=9.80$, $p<0.001$), task phase ($F(3,297)=38.03$, $p<0.001$), and a two-way

interaction ($F(6,297)=4.57$, $p<0.001$). Planned comparisons revealed significance when controls were compared with deficit patients ($F(1,99)=18.54$, $p<0.001$), but not when they were compared with non-deficit patients ($p>0.1$). The difference also was significant between deficit and non-deficit patients ($F(1,99)=10.97$, $p<0.01$) (Table 3). As compared with controls and with non-deficit patients, deficit patients showed significantly more errors in the 3rd and 4th phase of the task ($t>2$, $p<0.05$), but not in the retraining phase.

3.3. Correlations

None of the measures of frontal tests correlated with the number of errors in the training and probe phase of the “chaining” task ($r<0.1$). Similarly, correlations between frontal test measures and PANSS scores were not significant, although they showed a consistent trend across negative and general symptoms ($0.2>r>0.1$), that is, more severe negative and general symptoms were associated with worse test performances. A single significant correlation was found between training phase errors on the “chaining” task and negative symptoms ($r=0.33$, $p<0.05$). Negative symptoms accounted for 10.9% of variance in the case of training phase performance ($F(1,64)=7.84$, $p<0.05$), whereas it was only 1.4% in the case of probe phase performance ($p>0.1$).

4. Discussion

The importance of neuropsychological dysfunctions is widely recognized in schizophrenia, as exemplified by the MATRICS approach (Nuechterlein et al., 2004). However, traditional neuropsychological domains are too broad, less consistently defined, and hard to link to specific brain circuits. Therefore, a new initiative, called CNTRICS (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia), has been raised in order

Table 3
Results from the “chaining” task

	Controls (<i>n</i> =30)	Non-deficit (<i>n</i> =45)	Deficit (<i>n</i> =27)
Probe score	1.6 (1.2)	4.3 (3.8)*	4.6 (2.9)*
Training summary score	1.5 (0.9)	1.9 (4.1)	3.0 (1.4)**
Training at the 4 phases (rooms 1–4)	1.0 (0.8)	0.8 (0.8)	1.0 (0.7)
	1.6 (1.5)	2.0 (1.7)	2.7 (1.7)
	1.4 (1.0)	2.1 (2.9)	3.7 (2.2)**
	2.1 (1.5)	2.7 (2.6)	4.5 (3.0)**

The table contains the number of errors in each phase of the “chaining” task. Values are mean (standard deviation). *Significant difference compared with controls; **Significant difference compared with controls and with non-deficit patients (*t*-tests, $p<0.05$; for detailed statistics, see the text).

to define more discrete cognitive functions and related neuronal systems (Geyer and Carter, 2007). In this study, we used this approach to revisit the cognitive characteristics of the deficit syndrome. Using the “chaining” cognitive sequence learning test, which allows the within-task dissociation of habit and context learning, we demonstrated a specific cognitive dysfunction in deficit patients. This is not consistent with our initial hypothesis, assuming that deficit patients would show generalized impairments on the “chaining” task. Whereas impaired context representation was uniformly present in both non-deficit and deficit patients to a similar extent (deficit patients did not show significantly more severe impairment than non-deficit patients on the probe phase), habit learning was significantly compromised only in patients with deficit syndrome. This may suggest prominent impairments of the BG-dependent habit learning system in deficit syndrome.

The finding that context representation is impaired in schizophrenia is consistent with the literature. Dysfunctions of context representation are regularly mentioned in relation to working memory, executive functions, and declarative memory (Danion et al., 1999; Javitt et al., 2000; Perlstein et al., 2003). In the “chaining” task, however, context is gradually acquired during the learning of stimulus–response associations. The context-dependent probe phase of the task is most likely to be related to the MTL, including the hippocampus (Nagy et al., 2007a). This brain region has extensively been investigated with various functional, structural, neurochemical, histological, and molecular methods, and strong evidence suggests its marked impairment in schizophrenia (Goldman and Mitchell, 2004; Heckers, 2001; Weinberger, 1999). However, our data may suggest that the functioning of the MTL is not more compromised in deficit patients than in non-deficit patients, which is consistent with functional neuroimaging findings (Heckers et al., 1999).

Cognitive skill and habit learning, which is primarily related to the BG, is less extensively investigated in schizophrenia (Kéri et al., 2000, 2005a,b; Waltz et al., 2007; Weickert et al., 2002). Although habit learning may be relatively spared as compared with declarative and working memory, a recent study found subtle impairments in the processing of positive feedback (Go-signal) in a reinforcement learning task (Waltz et al., 2007). Juckel et al. (2006) used a reward anticipation task and measured fMRI responses in the limbic striatum of schizophrenia patients. These authors found that patients treated with second-generation antipsychotics and healthy control participants showed increased signals in the limbic striatum in response to reward indicating cues. In contrast, patients receiving first-generation drugs did not show such

responses. Blunted responses in the limbic striatum also were related to negative symptoms. These results raise two important issues. First, high doses of first-generation antipsychotics may disrupt BG circuits, which are responsible for feedback processing, reinforcement, and habit learning. Consistently with this assumption, Beninger et al. (2003) found impaired habit learning in patients receiving first-generation antipsychotics and intact habit learning in patients who were on second-generation drugs. Kéri et al. (2005a) demonstrated that patients receiving high doses of first-generation antipsychotics performed more poorly on a stimulus–response learning task, similarly to patients with Parkinson’s disease (Myers et al., 2003). A major limitation of this study was that a sufficient number of unmedicated patients were not included and the effect of different medications was not compared. These should be clarified by further studies.

The second question is related to negative symptoms, which were important predictors of “chaining” task performance. It is possible that patients with more severe negative symptoms, especially as seen in the case of primary negative symptoms of the deficit syndrome, are less able to process positive feedback and reinforcement, which results in impaired learning of stimulus–response chains. Similarly to our data revealing an inverse relationship between negative symptoms and stimulus–response learning, Waltz et al. (2007) found a moderate negative relationship between the total proportion of correct choices during the acquisition phase of a reinforcement learning task and negative symptoms, as measured with the Scale for the Assessment of Negative Symptoms (SANS) ($r = -0.37$).

There is some evidence that habit learning dysfunctions are related to decreased dopaminergic signal, probably in the BG. First, patients with Parkinson’s disease showed pronounced improvement on the “chaining” task after L-dopa substitution (Shohamy et al., 2005). Second, healthy subjects with lower plasma homovanillic acid levels (a metabolite of dopamine) displayed more errors in the training phase (Nagy et al., 2007b). Finally, subjects carrying a Parkinson’s disease risk haplotype of the alpha-synuclein gene, which regulates dopaminergic transmission, performed less efficiently on the training phase of the “chaining” task (Kéri et al., 2007). These findings suggest that decreased dopaminergic transmission is related to a less efficient learning of chaining associations. This is consistent with the inverse relationship between negative symptoms and “chaining” task performance, because in Grace’s dopaminergic model of schizophrenia, low basal dopamine levels are related to negative symptoms (Moore et al., 1999).

The relationship between habit learning and working memory is another important issue, because both are mediated by frontal-striatal circuits. However, evidence from basic sciences and animal research suggests that these functions are related to different frontal-striatal circuits (Yin and Knowlton, 2006; see also Frank, 2005), and data from schizophrenia patients, including the present ones, also indicate little relationship between higher level cognitive functions and habit learning (Kéri et al., 2005a; Waltz et al., 2007; Weickert et al., 2002). This is consistent with our initial hypothesis. It is important to note, however, that our “frontal” tasks may not be optimal to compare with sequence learning. Traditional tasks involving sequencing would be more relevant. This question must be addressed using more extensive cognitive testing and direct measurements of brain activation.

In conclusion, in this study, we found a compelling and specific difference between the neurocognitive profile of deficit and non-deficit patients, which may strengthen construct validity and may shed new light on the pathophysiology of the deficit syndrome.

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Contributors

All authors contributed to the basic idea of the study. Drs. Kelemen, Réthelyi, Bitter, Myers, Gluck, and Kéri designed the study and wrote the protocol. Drs. Myers, Gluck, and Kéri contributed to the development and validation of the test and its neuronal correlates. Drs. Kéri, Polgár, Farkas, and Nagy managed the literature searches and analyses. Dr. Polgár, Farkas, Nagy, and Kelemen performed the technical parts of the experiment. Dr. Kéri undertook the statistical analysis, and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

None.

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