Neuropsychological impairments in schizophrenia: focus on interactive memory systems and attention

Theses of doctorial dissertation

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INTRODUCTION

Cognitive impairments in schizophrenia are present at the onset of the illness, persist throughout the lifespan, are strongly associated with functional disability, and are largely treatment refractory. The fundamental cognitive deficit may exist within the mechanisms of **executive functions, attention, information processing and episodic memory.** The limbic system, hippocampus, PFC, parietal cortex, anterior cingulate cortex and basal ganglia have substantial role in memory in attention and mediate cognitive symptoms in schizophrenia that may result in disease psychopathology. The past decade has seen a rapidly growing understanding of the neurobiology and neuropharmacology of cognition in the domains of human and animal cognitive neuroscience. Establishing **patterns between neuropsychological performance and psychopathological dimensions** may shed light into underlying mechanisms of psychotic disorders. Despite the fact that the majority schizophrenia patients perform poorly on most laboratory tasks of cognition, the results from cognitive neuropsychiatry are highly controversial, which is partly due to the heterogeneity of the illness, decreased motivation, distractibility, slowness, and generalized intellectual disabilities, partly due to shortcomings and heterogeneity of current methods.

1. Memory dysfunction is one of the most consistently reported cognitive abnormalities. Literature in memory research in schizophrenia consistently reports a dominant abnormal episodic encoding and less but still impaired episodic retrieval, while semantic memory and recognition seem to be spared. The issue of memory impairment in schizophrenia is further complicated by the existence of interacting and dissociable memory systems in the brain: the **medial temporal lobe** is thought to be important in explicit learning and remembering, as a crucial part of the declarative memory system, which is important in the conscious acquisition and recollection of facts and events. Hippocampus and related MTL may be important for the ability to generalize the learned information. In contrast, many non-declarative (implicit) memory functions, such as gradual learning of skills and habits (based on stimulus-response, sequence and category learning) are linked to the basal ganglia. Memory systems detailed above are organized in a tightly interactive manner, thus processing and representation of information may

take place in **multiple and interacting structures in the brain**, with special reference to the prefrontal cortex (PFC), basal ganglia and medial temporal lobe.

Contrary to declarative memory research in schizophrenia, nondeclarative memory has been considerably less studied. This *aspect of memory seems to be relatively preserved,* but the results are somewhat controversial and the majority of studies proving intact habit learning used classic sensorimotor tasks. Despite the fact that pathophysiology of schizophrenia could be further elucidated by investigation of interaction between prefrontal cortex, MTL and BG in memory systems, memory systems in schizophrenia has not been yet deeply explored, partly due to lack of behaviour paradigms and the shortcomings of existing procedures. Most widely used neuropsychological tests in schizophrenia research target the MTL–dependent declarative memory system, whereas the BG non-declarative memory system is less frequently investigated due to lack of "pure" cognitive paradigms. There is no published study in schizophrenia 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. Therefore, introduction of novel behavioural paradigms in memory research is still warranted.

Motivated by the above-mentioned needs, we introduced two novel methods that can serve as a useful tool for studying memory systems. We tested the **cognitive sequence learning task** in healthy volunteers in order to elucidate the role of dopamine in sequence learning or chaining tests, where the enhancing role of L-dopa was confirmed in a population of Parkinson's patients. We also introduced the **Rutgers Acquired Equivalence Test** in order to investigate declarative and non-declarative memory systems within the same paradigm in schizophrenic patients. The Rutgers acquired equivalence associative learning task 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.

2. **Attention deficit** is thought to be a core feature of schizophrenia, which contributes to impairments in community functions and represent a vulnerability marker

for psychosis. Surprisingly few studies explored the nature and mechanism of this deficit regarding the current theoretical frameworks of attention. Posner and Petersen (1990), postulates that sources of attention form a specific system of anatomical areas, which can be further divided into three networks (alerting, orienting and executive control). These three networks are differently impaired in schizophrenia and different researches suggest an attention control deficit in the disorder with impairment of lateral prefrontal areas, anterior cingulate cortex, and parietal lobes. However, the findings in attention deficit in schizophrenia are also controversial, partly due to different concepts of attention. There is also a methodological problem in this issue, since measurements of attention functions are based on tasks that are not process pure but also tend to require a range of other cognitive capacities. Thus, introduction of novel paradigms to investigate different aspects off attention is also warranted, with special foculs of attention control functions.

Many typical everyday activities, such as simultaneously watching people in a crowd, or navigating in heavy traffic, require attention to multiple locations of the environment. These functions, which model real-life attention demands more reliably that traditional laboratory task, have not been investigated in schizophrenia. Pylyshyn and Storm were the first to experimentally demonstrate that participants are able to continuously track multiple moving objects using multiple-object tracking (MOT) test. Evidence suggests that visual working memory and motion perception that are related to each other are indispensable for successful multiple-object tracking. Since patients with schizophrenia are impaired on tests of motion perception and visual working memory, running multiple-objects tracking task in schizophrenic patients may provide a tool for concurrent investigation of not only the tightly connected working memory but the sensory (input) system and attention as well. We hypothesize that patients with schizophrenia are less efficiently able to track multiple moving objects. Many studies demonstrated correlations between negative symptoms and cognitive dysfunctions in schizophrenia; therefore it seems to be worth investigating whether negative symptoms are related to multiple-object tracking performance in schizophrenia.

OBJECTIVES

Motivated by recent advantages and challenges detailed above, the thesis was designed for the following purposes. First, to identify the role of dopamine in cognitive

habit learning in order to find a new paradigm that can be serving as a useful tool in memory research in different neuropsychological disorders including schizophrenia. Second, we aimed to investigate different aspects of neuropsychological deficit in schizophrenia using novel paradigms, with special focus on memory and attention. The summary of the experiments are presented in Table 1., with a short description of the objectives, participants, employed procedures, main findings and conclusions.

METHODS

Participants

All participants in the studies gave written informed consent **and they** were screened with Mini-International Neuropsychiatric Interview. General intellectual functions were measured by Wechsler Adult Intelligence Scale. In SCZ patients, clinical symptoms were assessed with the Positive and Negative Syndrome Scale. SCZ patients were chronic outpatients and did not show acute psychotic symptoms. Chlorpromazine-equivalent dose of antipsychotics was calculated in patients taking antipsychotic medication. Educational, family and medical history including neurological disorders, head injury, substance abuse, electroconvulsive therapy was collected as well for both healthy and SCZ population. Hollingshead Four-Factor Index was employed for assessment of socioeconomic status in the experiment 1. In experiments 2. and 3., there were no significant differences between patients and controls in age, years of education, and IQ.

Neurological disorders, substance dependence, history of head injury, electroconvulsive therapy, and central nervous system disorders due to general medical conditions were the exclusion criteria. In experiment 1., exclusion criteria were also any other medical condition that can affect central nervous system functions (cardiac, renal, hepatic, metabolic, and hormonal illnesses), and all participants were non-smokers and did not take any medication. In the experiment 1., plasma levels of metabolites were measured using the coulochem electrode array system. Measurements included the levels of homovanillic acid [HVA] (a metabolite of dopamine), 5-hydroxyindoleacetic acid [5-HIAA] (a metabolite of serotonin), and 3-methoxy-4-hydroxypheylglycol [MHPG] (a metabolite of norepinephrine).

Table 1. Summary of experiments

EXPERIMENT	OBJECTIVES	PARTICIPANTS	PROCEDURE	MAIN FINDINGS	CONCLUSIONS
Experiment 1. **Dopaminergic contribution to cognitive sequence learning**	1. Elucidate specific role of dopamine in cognitive sequence learning, by measuring the metabolite of dopamine, serotonin, and norepinephrine in the plasma of healthy volunteers. 2. Find correlations between neurochemical markers and performance on the "chaining" sequence-learning task.	n=125 healthy people (70 male) • M.I.N.I. • Education • Hollingshead Four-Factor Index • WAIS-R	1. Cognitive sequence learning 2. Plasma levels of: • homovanillic acid [HVA] (a metabolite of dopamine), • 5-hydroxyindoleacetic acid [5-HIAA] (a metabolite of serotonin) • 3-methoxy-4-hydroxypheylglycol [MHPG] (a metabolite of norepinephrine).	1. Significant negative relationship between errors in the feedback-guided training phase and the plasma HVA level but not with 5-HIAA and MHPG levels. 2. Participants under sample median HVA level committed more errors during the training phase, but not in probe phase.	Dopamine plays a special role in feedback-guided cognitive sequence learning.
Experiment 2. Dissociation between medial temporal lobe and basal ganglia memory systems in schizophrenia	1. Investigate the BG and MTL –dependent learning in patients with schizophrenia. 2. Find possible relationship between acquired equivalence learning and conventional measures of declarative and working memory, and 3. antipsychotic medication.	SCZ=43 (29 male); paranoid (n=12), undifferentiated (n=16), residual (n=11), disorganized (n=4) CO= 28 (17 male) • SCZ diagnosis based on DSM-IV criteria • M.I.N.I. • PANSS	1. Rutgers acquired equivalence task 2. California Verbal Learning Test (CVLT) 3. n-back working memory test.	1. SCZ patients showed a selective deficit on stimulus generalization but not in stimulus–response learning 2. The stimulus generalization deficit correlated with the CVLT performance, but not with the n-back test performance. 3. The number of errors during stimulus–response	1. Assessed within a single task, patients with SCZ exhibit deficits during MTL-dependent learning, but not during BG-dependent learning. 2. High-dose first generation antipsychotics may disrupt BG-dependent learning by blocking dopaminergic

EXPERIMENT	OBJECTIVES	PARTICIPANTS	PROCEDURE	MAIN FINDINGS	CONCLUSIONS
		• Education • WAIS-R • medication		learning correlated with the daily chlorpromazine-equivalent dose of antipsychotics.	neurotransmission in the nigro-stiratal system
Experiment 3. **How can patients with schizophrenia track multiple moving targets**?	1. Investigate MOT in patients with schizophrenia. Investigate the contribution of 2. positive and negative symptoms, 3. velocity discrimination, 4. sustained attention/context processing, 5. visual working memory to multiple-object tracking performance.	SCZ=30 (21 male);(18 paranoid, 6 undifferentiated, 4 residual, 2 disorganized) CO=30 (21 male) • SCZ diagnosis based on DSM-IV criteria • M.I.N.I. • PANSS • Education • WAIS-R • medication	1. Fast and slow multiple-object tracking (MOT) 2. Motion perception (velocity discrimination) 3. Continuous Performance Test, 1-9 version, 4. Object working memory, 5. Spatial working memory.	1. Patients wit SCZ displayed impaired performances on MOT tasks. 2. No correlation between MOT performance and negative symptoms in SCZ. 3. In patients with SCZ, velocity discrimination and spatial working memory were the predictive factors of multiple-object tracking. 4. Continuous Performance Test made significant contribution to discriminating between patients and controls.	1. MOT is impaired in schizophrenia 2. MOT is specifically associated with motion perception and spatial working memory. 3. MOT dysfunction might be related to a complex cortical network including motion-sensitive regions (V5) and areas responsible for spatial processing (posterior parietal cortex), eye movements, and working memory (prefrontal cortex, including the frontal eye field).

Table 1. continued

Statistical methods

The STATISTICA 6.0 package (StatSoft, Tulsa, OK) was used for data analysis. The distribution of the data was checked with Kolmogorov-Smirnov tests, and the homogeneity of variance was checked with Levene`s tests. If normal distribution and homogeneity of variance were proven, the dependent measures were compared with two-tailed t-tests or ANOVA, followed by post hoc or F-tests. In other cases Mann-Whitney U-test were applied. Linear and multiple regression analyses were used for measurement of predictive factors and we calculated correlations using by Pearson r and Spearman R. The level of significance was set at alpha<0.05. Effects sizes (Cohen's *d*) were also given in experiment 3.

Experimental procedures

Only a brief introduction of newly employed test methods can be provided here.

1. During computer based **"chaining" or cognitive sequence learning task**, each link in a sequence of stimuli leading to reward is trained step-by-step using feedback after each decision, until the complete sequence is learned. In the first phase of this task, the screen showed a room (room 1) with three doors (A, X, Y), each bearing a coloured card; the participant was required to choose one of these doors. A correct response (door A) led to a treasure chest (reward), while an incorrect response (X or Y) led to a brick wall. Once this A→reward association was learned, participants were presented with another room (room 2) with three new coloured doors (B, W, Z). An incorrect response (W or Z) led to a brick wall, while a correct response (door B) led to room 1, where subjects 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. The test consist of four phases: 1. "practice" where participants learn a simple stimulus-response association; 2. "sequence training" where participants learn the full sequence; 3. "probe phase" where the aim is to ascertain that participants learned the correct door in its correct place in the sequence and 4. "retraining phase" in order to determine whether any learning deficits observed on the sequence learning or probe phase could be due to fatigue effects or other nonassociative factors.

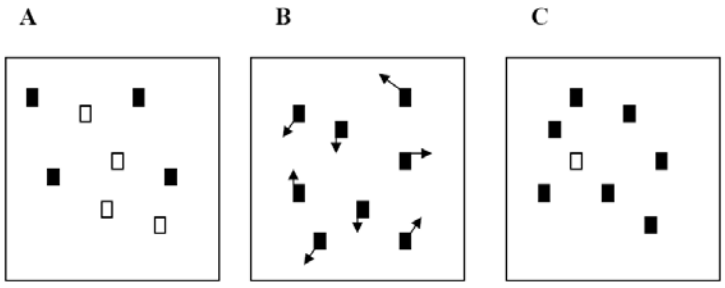
2. The **Rutgers acquired equivalence associative learning task** is also computer based. Acquired equivalence is a phenomenon in which prior training to treat two stimuli as equivalent (if two stimuli are associated with the same response) increases generalization between them (Table 2). In the acquisition phase of the task, participants learn six pairs of stimulus-response associations. The stimuli are cartoons of persons' faces and colour fishes and each person is associated with fishes with different colours. The learning of stimulus-response pairs is related to the BG, whereas the MTL system participates in acquired equivalence learning (transfer phase).

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 A2 – X1	A1 – X1 A2 – X1 A1 – X2	A2 – X2?
B1 –Y1	B1 – Y1 B2 – Y1	B1 – Y1 B2 – Y1 B1 – Y2	B2 – Y2?

3. In the computer based multiple-object tracking (MOT) test, identical squares randomly move within a rectangular area, bouncing off the borders and each other. Participants are asked to follow some selected squares (target items) embedded in a group of distracters. At the end of a trial, a square is marked and participants report whether or not the square is one of the target items (Figure 1.). There were two velocity conditions: (i) an average velocity of 6.4°/sec (slow condition); (ii) an average velocity of 8.4°/sec (fast condition).

Figure 1. The multiple-object tracking test



RESULTS

Experiment 1.

The mean plasma levels of metabolites were as follows: HVA: 7.1 ng/ml (SD=2.5), 5-HIAA: 1.5 ng/ml (SD=0.9), MHPG: 3.8 ng/ml (SD=1.2). **There was a significant negative relationship between the mean number of errors in the training phase of the "chaining" task and the HVA level (R=-0.36, p<0.05).** In contrast, the HVA level did not correlate with the number of errors in the probe phase of the "chaining" task (R=0.01). 5-HIAA and MHPG levels did not correlate with the "chaining" task measures ($r<0.1$). Linear regression analysis revealed that the HVA level accounted for 10.5% of variance of training phase errors ($F(1,118)=13.9$, $p<0.001$). In the case of 5-HIAA and MHPG, this value was less than 1% ($p>0.5$). A median-split analysis was also performed. Participant who had lower HVA plasma level than the median value of the whole sample committed more errors during the training phase of the "chaining" task compared with participants who has higher HVA plasma level than the median value ($t(118)=-3.12$, $p=0.002$). This difference remained significant when age, gender, education, socioeconomic status, and IQ were included in an analysis of covariance ($F>8$, $p<0.05$). In contrast, the median-split analysis did not indicate differences between participants with low and high HVA in the probe phase ($p=0.72$). As expected from the correlation analysis, median-split analyses for 5-HIAA and MHPG did not indicate differences between participants with low and high level of metabolites ($p>0.5$). *There was no significant difference in IQ between participants with low HVA (mean: 105.6 (SD=10.8)) and high HVA (mean: 104.9 (SD=11.3)) (p>0.5).*

In order to further elucidate the relationship between HVA and sequence learning, we analyzed the number of errors in each step of the chain of associations (room 1-room 4 in the training phase). An analysis of linear trend revealed that the number of errors linearly increased as a function "chaining" associations in participants with low HVA ($F(1,118)=30.23$, $p<0.001$). This relationship was less pronounced in participants with high HVA ($F(1,118)=4.47$, $p=0.04$), and the interaction for linear trend between participant with low and high HVA approached the level of significance ($F(1,118)=3.21$, $p=0.07$). Participants with low HVA committed significantly more errors at the third association (phase 3) ($t(118)=3.0$, $p=0.002$). Finally, participants with low and high

HVA did not differ in the retraining phase (mean number of errors: 1.1 (SD=0.8) and 1.2 (SD=0.9), respectively ($p>0.5$))

Experiment 2.

The mean number of errors during the acquisition phase was 8.8 (SE=1.2) in the schizophrenia group and 7.7 (SE=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 (SE=0.02) in the schizophrenia group and 0.08 (SE=0.02) in the control group. The mean proportion of errors for new associations was 0.41 (SE=0.04) in the schizophrenia group and 0.13 (SE=0.03) in the control group*. An analysis of variance (ANOVA) conducted on the error rates *for new and old associa*tions 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. 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 $r=0.76$, $p<0.05$).

Experiment 3.

Patients with schizophrenia showed impaired performances on the velocity discrimination test, CPT, and object and spatial working memory tasks. They were similarly impaired on the fast and slow multiple-object tracking tests. The *d*-statistics revealed large effect size values. In the control group, the single predictive factor for fast multiple-object tracking performance was the velocity discrimination threshold (beta=-0.44; $F(1,28)=10.87$, $p<0.005$; $R^2=0.28$). In the patients with schizophrenia, fast multiple-object tracking performance was predicted by velocity discrimination (beta=-0.45; $F(1,28)=10.98$, $p<0.005$; $R^2=0.28$) and spatial working memory (beta=-0.42; $F(1,28)=12.26$, $p<0.005$; $R^2=0.30$). In the slow condition, only spatial working memory predicted multiple-object tracking performances (beta=-0.40; $F(1,28)=7.32$ $p<0.05$; $R^2=0.21$). The regression analysis including the PANSS-scores, the duration of the illness, and the chlorpromazine-equivalent dose of antipsychotics did not reveal a significant effect ($p>0.1$). The probabilistic regression analysis indicated that only the CPT made significant contribution to predicting group membership (patients with schizophrenia vs. controls) (beta=-0.27, $F(1,28)=10.48$, $p<0.005$; $R^2=0.15$).

CONCLUSIONS

Experiment 1.

Our results indicate that sequence learning is specifically related to dopaminergic functions, which is consistent with previous data from patients with PD. HVA level selectively correlated with the number of error in the training phase of the “chaining” task, but not with the performance in the probe phase. Recent data indicate that the training and the probe phases of the “chaining” task are neuropsychologically dissociable. In contrast to patients with PD, patients with medial temporal lobe damage can efficiently complete the training phase and can learn the sequence of associations but display many errors during the probe phase, which is not seen in patients with PD. The current neurochemical data support this dissociation, because dopamine metabolism was related only to the training phase of the “chaining” task. Functional imaging data show that feedback during a cognitive task activates striatal and frontal regions, which receive input from midbrain dopaminergic neurons, and midbrain activity is related to coding of the "prediction error". Thus, functional neuroimaging data, together with result from PD

and from our neurochemical study, support the role of dopaminergic mechanisms in feedback-guided skill and habit learning.

Experiment 2.

The findings of this study indicate that patients with schizophrenia are impaired on tests of MTL-dependent learning, whereas BG-dependent learning is spared. This latter observation is consistent with the results of two previous studies, demonstrating intact BG-dependent cognitive skill learning in schizophrenia. 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. 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. In our study, subcortical memory functions did not show a robust impairment in contrast to hippocampal stimulus generalization, which is against the concept of 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. 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.

Experiment 3.

The main finding of our study was that patients with schizophrenia performed poorly on the multiple-object tracking test. These results are consistent with previous studies demonstrating that patients with schizophrenia are impaired when two concurrent tasks must be monitored. Our data also suggest that impaired multiple-object tracking performance in schizophrenia is not a mere consequence of clinical symptoms, generalized cognitive impairment, medication effects, impaired sustained attention/context processing (CPT), or impaired object working memory. Specifically, we demonstrated circumscribed relationships among multiple-object tracking*, processing of motion and speed (velocity discrimination), and spatial working memory*. Contrary to our expectations, multiple-object tracking performance was not related to the negative symptoms of schizophrenia and it is consistent with other findings.

We hypothesize *that the dysfunction of the cortical network related to motion perception and spatial working memory may play an important role in multifocal attention dysfunctions in schizophrenia. The dysfunction of multiple-object tracking might be related to a complex cortical network including motion-sensitive regions (V5) and areas responsible for spatial processing (posterior parietal cortex), eye movements, and working memory (prefrontal cortex, including the frontal eye field).* Further studies are warranted to investigate the complex relationship among low-level sensory processes, different domains of attention, and multiple-object tracking functions in normal and pathological conditions.

In summary, based of our results, our conclusions are as follows:

1. Dopamine plays a special role in feedback-guided cognitive sequence learning. The chaining test as a novel, based on lesion and neurochemical results, may provide a new tool for assessing habit learning and multiple, cooperative memory systems in different neuropsychiatric populations.

2. Patients with schizophrenia exhibit deficits during MTL-dependent learning, but not during BG-dependent learning, measured by a novel method (RTET) that eliminates psychometric artefacts; and high-dose first generation antipsychotics may disrupt BG-

dependent learning by blocking dopaminergic neurotransmission in the nigro-stiratal system;

3. Multiple-object tracking is impaired in schizophrenia, and the possibile underlying deficit in complex cortical networks including motion sensitive and prefrontal and posterior parietal areas provide inspiration for further research.

Concerning the "widespread cortical dysfunction hypothesis" of schizophrenia, our new findings about disturbed complex cortical networks and lower level sensory processes, may provide new insights into the pathophysiology of the disorder.

Despite the limitations such as small sample size, absence of electrophysiological, neuroimaging or genetic testing, our data stress the importance of defected cognitive domains in schizophrenia that play important role in functionality, highlight the role of antipsychotic medication in different learning processes and finally, may serve as an input in complex psycho-social rehabilitation strategies.

LIST OF PUBLICATIONS

List of publications related to the thesis

First author

1. **Nagy O**, Kelemen O, Benedek G, Myers CE, Shohamy D, Gluck MA, Kéri S. (2007). Dopaminergic contribution to cognitive sequence learning. J Neural Transm. 114(5):607-12.
2. **Nagy O**, Kelemen O, Erdélyi R, Pataki M, Janka Z, Myers CE, Gluck MA, Kéri S. (2005). Tanult ekvivalencia a szkizofréniában: új módszer a hippocampalis és basalis ganglionokhoz kapcsolódó memóriafunkciók mérésére. [Learned equivalence in schizophrenia: novel method for the measurement of memory functions of the hippocampus and basal ganglia]. Psychiatr Hung. 20(5):363-9.

Non first author

1. Kéri S, **Nagy O**, Kelemen O, Myers CE, Gluck MA. (2005). Dissociation between medial temporal lobe and basal ganglia memory systems in schizophrenia. Schizophr Res. 15;77(2-3):321-8.
2. Kelemen O, **Nagy O**, Mátyássy A, Bitter I, Benedek G, Vidnyánszky Z, Kéri S. (2007). How well do patients with schizophrenia track multiple moving targets? Neuropsychology. 21(3):319-25.
3. Polgár P., Farkas M., **Nagy O.**, Kelemen O., Réthelyi J., Bitter I., Myers CE., Gluck MA., Kéri S. (2007). [Learning cognitive skills in depression: the effect of context-change] Psychiatr Hung. 22(4):271-5.
4. Polgár P., Farkas M., **Nagy O.,** Kelemen O., Réthelyi J., Bitter I., Myers CE., Gluck MA., Kéri S. (2008). 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. Schizophr Res. 99(1-3):200-7.

Posters:

1. Kelemen O., **Nagy O.,** Máttyássy A., Kiss I., Janka Z., Kéri S. (2006). Do second-generation antipsychotics disrupt decision-making abilities in schizophrenia? Poster presented: ECNP Congresss, Paris, France, 16-20 Sep 2006. Poster Nr.: P3d002.
2. Kelemen O., Máttyássy A., **Nagy O.,** Myers C., Janka Z., Gluck M., Kéri S. (2006). Basal ganglia and medial temporal lobe memory systems in schizophrenia: the effect of antipsychotics. The International of Neuropsychopharmacology. 9; Suppl.1, S148. p., 2006. Poster presented: XXV. CINP Congress, Chicago, 9-13 July 2006.
3. Kéri S, Kelemen O, **Nagy O,** Vidnyánszky Z, Bitter I, Benedek G. (2007). Multiple-object tracking in patients with schizophrenia and in people at high risk of schizophrenia. Schizophrenia Bulletin 2007; 33: 527. Poster presented: 11th International Congress on Schizophrenia Research, Colorado Springs, Colorado, USA. 28 March – 01 April 2007.

List of other publications

Written publication:

1. Szűcs A., **Nagy O**., Kákonyi Z., Mlinarics R. (2003). Sürgősségi pszichiátriai ellátás a háziorvosi gyakorlatban. Háziorvos Továbbképző Szemle.7:544-8.

Poster

1. Nagy B., Bowrin K., Lloyd A., Mungapen L., Van Baardewijk M., Kutikova L., **Nagy O.,** Bánki MCs., Bitter I. (2009). Cost-minimalisation analysis of aripiprazole in the treatment of bipolar disorder in Hungary. Poster presented: 15th Congress of Hungarian Psychiatric Association. Hungary, Debrecen. 28-31 January, 2009.

ABBREVIATIONS

CPT: Continuous Performance Test

CPZ: Chlorpromazine-equivalent Dose of Antipsychotics (mg/day)

CO: healthy control

CVLT: California Verbal Learning Test

DA: dopamine

DL-PFC: dorsolateral prefrontal cortex

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition

HVA: Homo-vanillic Acid

IQ: Intelligence Quotient

MHPG: 3-methoxy-4-hydroxyphenylglycol

M.I.N.I.: Mini-International Neuropsychiatric Interview

MOT: Multiple Object Tracking

MTL: Medial Temporal Lobe

p: Probability

PANSS: Positive and Negative Syndrome Scale

PD: Parkinson's disease

PFC: Prefrontal Cortex

r: Pearsons' Correlation Coefficient

R: Spearman's Correlation Coefficient

SCZ: schizophrenia

SD: Standard deviation

SE: Standard Error

VL-PFC: ventrolateral prefrontal cortex

WAIS-R: Wechsler Adult Intelligence Scale, revised