Visual and Cognitive Processes in Schizophrenia

Summary of Ph.D. Thesis

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Abbreviations

BD: Bipolar disorder

CPT: Continuous Performance Test

fMRI: functional magnetic resonance imaging

HD: High distortions

ISI: Inter-stimulus interval

LD: Low distortion

MMSE: Mini-Mental Sate Examination

M: Magnocellular

P: Parvocellular

PCL: Probabilistic classification learning

SCZ: Schizophrenia

STS: Superior Temporal Sulcus

ToM: Theory of Mind

VBM: Visual backward masking

WAIS-R: Wechsler Adult Intelligence Scale, revised

WCST: Wisconsin Card Sorting Test

1. Summary

Schizophrenia is often conceptualized as a complex disorder of cognition (Frith, 1992; Braff, 1993; Goldman-Rakic, 1994; Andreasen, 1999; Weinberger et al., 2001). Besides progress in the discovery of neuronal bases of impaired cognition, recent evidence suggests that cognitive dysfunctions may have direct clinical relevance. First, disordered cognition have a substantial impact on the quality of life and social reintegration of the patients (Green, 1996). Second, cognitive dysfunctions are detectable in unaffected biological relatives of schizophrenia patients, which raises the possibility that they may facilitate the elucidation of genetic mechanisms and may be useful in early detection of psychosis (Kéri and Janka, 2004).

Motivated by the above described issues, this thesis was designed to investigate cognitive processes in schizophrenia from early-stage visual perception to social cognition. First, we examined how simple visual categories are acquired and represented in patients with schizophrenia. We show that category learning functions related to repetition priming (prototype learning) and cortico-striatal interactions (probabilistic classification learning (PCL)) are spared in schizophrenia in contrast to category learning based on executive functions (Wisconsin Card Sorting Test (WCST)). Second, we assessed rapid sensory processing by the visual backward masking (VBM) paradigm. We found that VBM dysfunctions, especially when the spatial location of briefly flashed targets must be detected, may be more sensitive and specific markers of schizophrenia compared with working memory/executive dysfunctions. Third, it is revealed that critical aspects of social cognition concerning the representation of mental states ("Theory of Mind" (ToM)) is closely related to specific alterations in motion perception, but not to general intellectual functions (IQ).

These results suggest that dysfunctions in the processing of rapid temporal changes of brief duration, fast offset, sequential sensory interaction, and motion are fundamental aspects of the neurocognition of schizophrenia, which is observable in remitted patients and in healthy siblings of schizophrenia patients. These can be conceptualized in the framework of retino-geniculo-occipital magnocellular (M) and parvocellular (P) visual pathways and their cortical recipients in the dorsal and ventral visual stream and prefrontal cortex.

2. Introduction

Schizophrenia is one of the most devastating mental disorders. Because of its early onset and chronic course, patients and their caregivers must face with many years of relapsing-remitting clinical symptoms, lower quality of life, and impaired social reintegration. From a medical point of view, schizophrenia is an enigmatic and complex mental disorder with unknown origins. According to current estimates, the heritability of schizophrenia is about 60-80% with close interactions with environmental and social factors such as perinatal hypoxia, in utero viral infection and starvation, winter birth, immigration, urban living conditions, and high expressed emotions within affected families (McDonald and Murray, 2000). The positive, disorganized, and negative symptoms involves nearly all domains of psychopathology, perception, thinking, affect, and self-regulation (Andreasen and Carpenter, 1993).

In the past decades, several theorists developed models in order to explain the symptoms on the basis of some fundamental cognitive deficit. Frith (1992) divided the symptoms into three dimensions (willed actions, self-monitoring and ToM deficits). Another theory is based on single cell studies in non-human primates by Goldman-Rakic (1994). This suggests that the fundamental impairment of schizophrenia is an inability to guide behavior by active, short-term internal representations (working memory). This theory is closely related to the work of Weinberger et al. (2001), who emphasize the physiological dysfunction of prefrontal cortical circuits and their connections with other brain structures, in particular the medio-temporal structures responsible for memory functions.

Braff and colleagues (1993) developed another complementary model, which is based on data from clinical and animal neurophysiology. They hypothesize that the core deficit of schizophrenia is the impairment of early-stage sensory processing and attention, which then induces disorganization in higher-level neuronal representations. This hypothesis led to the renaissance of the Bleulerian "schisis", a disconnection and functional de-coupling of a widely-distributed neuronal network (Andreasen, 1999).

Given that an accumulating number of evidence suggests the genetic factors play an essential role in the pathogenesis of schizophrenia, more attention has been paid to cognitive dysfunctions as endophenotypes. In general, endophenotypes (synonyms: trait markers, intermediate phenotypes, vulnerability markers) are cognitive-behavioral, neurochemical, structural or functional abnormalities that are detected in clinically unaffected biological relatives of the patients, heritable, and associated with a candidate gene. These may provide

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simpler clues to genetic underpinnings than the disease syndrome itself, suggesting that psychiatric diagnoses can be decomposed or deconstructed, which can result in more successful genetic analysis (Gottesman and Gould, 2003)

3. Questions addressed by the thesis

1. Recent evidence suggests that learning of visual prototypes and probabilistic categories are mediated by the sensory neocortex and the cortico-striatal connections, respectively (Gabrieli, 1998). These implicit learning mechanisms have not been explored in schizophrenia.

2. Rapid visual information processing was assessed by the visual backward masking paradigm (VBM) in remitted patients with schizophrenia-spectrum disorders and in siblings of patients with schizophrenia and bipolar disorders in order to investigate whether VBM dysfunction is an endophenotype of schizophrenia. The relationship between higher-level cognitive functions and VBM also was addressed.

3. We assessed "theory of mind" (ToM) functions in patients with schizophrenia and in their unaffected healthy relatives. The relationship between IQ, ToM, and motion perception was evaluated (for a summary outline, see Table 1).

4. Experimental procedures

The experimental procedures are well known from studies conducted on different patient samples and healthy control participants. Here only a brief description of the main procedures is given.

4.1. Prototype learning

Low and high distortions (LDs and HDs, respectively) of a prototype dot pattern were generated by various degrees of displacement of the dots. Unrelated (non-category) items were category-independent dot patterns (Figure 1). In the category learning experiment, 40 HDs were presented successively, each for 5 sec. To reduce conscious encoding, subjects were not informed that the training items belonged in the same category. After an unfilled delay period of 5 min, 4 prototypes, 20 new LDs, 20 new HDs, and 40 random patterns were presented in a pseudorandomized order. Participants were asked to press the "yes" key if the

testing item belonged in the training category and the "no" key if it did not (Reber et al., 1998).

Figure 1. Stimuli from the prototype experiment

Prototype Low High Unrelated
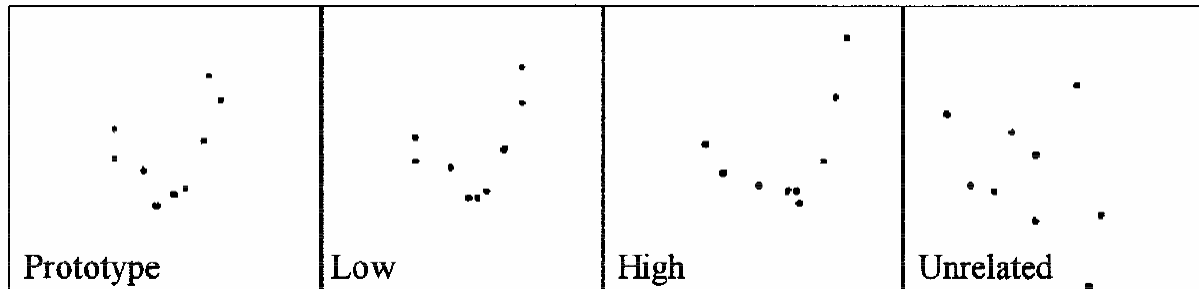
4.2. Probabilistic classification learning (PCL)

Subjects were requested to decide whether a pattern of cues predicted rain (category 1) or sunshine (category 2). Four cues were used, each comprising simple geometrical forms (circle, square, triangle, and rhombus). Each cue was associated with a particular weather outcome with a certain probability. In a trial, the experimenter presented 1, 2, or 3 cues. Subjects were asked to respond by deciding whether the cue(s) indicated rain or sunshine. After each trial, the experimenter provided a verbal feedback. Altogether 50 trials were included (5 blocks of 10 trials). Performance was defined as the percentage of correct responses, that is, selection of the weather outcome that was most probably associated with the presented cue(s) (Knowlton et al., 1996).

4.3. Visual backward masking (VBM)

In the target identification test, the task was to recognize a letter, while in the target location task, the spatial position of a letter was reported (Figure 2). Participants were exposed to a letter (C, O, Q, S), which appeared at one of four locations set at 2.5° of visual angle from the central fixation point (top, bottom, left, right). The task was to press the appropriate keys. The mask consisted of overlapping X letters, covering all possible target locations.

In the target identification test, the exposure time of the target was 14 ms, while that of the mask was 28 ms (high energy masking condition where the energy of the mask is defined as the light intensity x duration). In the target location test, the duration of the mask was identical to that of the target (14 ms). The interval between target offset and mask onset

(interstimulus interval, ISI) was set at 5 levels: 14, 28, 42, 70, and 98 ms. Twelve targets were presented at each ISI in a pseudo-randomized fashion (Green et al., 1994a,b).

Figure 2. The backward masking paradigm. Black dots indicate possible target locations. (ISI – interstimulus interval)
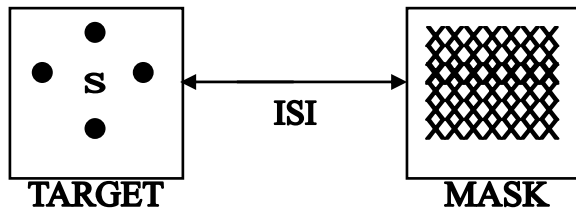
4.4. Eyes Test

The experimenter presented 29 photographs of the eye-region of faces of actors and actresses, each expressing different complex mental states. Subjects were asked to choose which of the four words (one target and three foils) best describes the mental state of the actor/actress (Baron-Cohen et al., 2001).

4.5. Motion and form coherence threshold

(A) Motion coherence: A proportion of dots in a middle strip oscillated in the opposite direction to those in the upper and lower strips. If a larger percentage of dots has to oscillate coherently to be detected, the motion coherence threshold is higher.

(B) Form coherence: Line segments are tangentially organized to comprise a circle. Tangentially oriented segments are embedded among randomly oriented segments. Form coherence threshold is defined as the percentage of tangentially oriented segments which is indispensable for the detection of the circle (Atkinson et al., 1997).

4.6. Background neuropsychology

The following general tests were used to supplement the above described procedures: (1) General intellectual functions: Wechsler's IQ; (2) Working memory/executive functions: Wisconsin Card Sorting Test (WCST), spatial working memory, span tasks, fluency tests; (3) verbal memory: short and long delay recall of word lists (Lezak, 1995).

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5. Results and discussion

Table 1. Summary of the experiments. Participants, related procedures, main findings and conclusions are shown for each experiment.

Experiment	Participants	Procedure	Main findings	Conclusions
Experiment 1	22 SCZ patients 20 controls	Prototype learning WCST MMSE	SCZ patients with impaired MMSE and WCST show intact prototype learning	Neocortical implicit learning is spared in SCZ
Experiment 2	30 SCZ patients 20 controls	Probabilistic classification learning	SCZ patients show normal learning	The cortico-striatal habit learning system is spared in SCZ
Experiment 3	15 remitted SCZ-spectrum patients 34 controls	Backward masking Spatial working memory WCST	SCZ-spectrum patients with spared working memory display masking deficits; target location is more affected	Rapid visual processing is a sensitive marker of SCZ; possible pathology of M pathways
Experiment 4	25 siblings of SCZ patients 20 siblings of BD patients 20 controls	Backward masking Spatial working memory Span tasks Fluency tests Verbal memory	Siblings of SCZ patients showed target location masking deficits; the recall of verbal information after long delay was impaired in both sibling groups	Rapid visual processing and M pathway dysfunction are endophenotypes of SCZ; fronto-hippocampal dysfunction is present in both sibling groups
Experiment 5	52 SCZ patients 30 controls	Eyes Test (ToM), Motion and form coherence threshold IQ	SCZ patients performed worse during the Eyes Test and the motion coherence; the Eyes Test deficit correlated with motion perception abnormality, but not with IQ	ToM dysfunctions are not related to general intellectual deficit, but to perceptual alterations affecting the M pathway/dorsal stream system
Experiment 6	79 relatives of SCZ patients 40 controls	Eyes Test (ToM)	The unaffected relatives performed normally during the Eyes Test	The ToM deficit is not an endophenotype of SCZ

SCZ – schizophrenia, BD – bipolar disorder, ToM – "theory of mind", MMSE – Mini-Mental State Examination, WCST – Wisconsin Card Sorting Test

The main results were as follows:

1. Patients with schizophrenia performed normally during cognitive skill learning (prototype and probabilistic classification learning). This suggests that despite profound impairments in executive (prefrontal) and explicit memory (medio-temporal) functions, schizophrenia patients have relatively well functioning sensory neocortical and cortico-striatal implicit representational systems.

2. Remitted patients with schizophrenia-spectrum disorders who had normal working memory/executive functions and highly functioning siblings of schizophrenia patients displayed significant deficits during VBM, in particular during the detection of target location. Siblings of patients with psychotic bipolar disorder had intact VBM performances. This suggests that rapid perception of transient and sequential visual information is a sensitive and specific endophenotype of schizophrenia, indicating the fundamental pathology of the M pathway/dorsal stream system.

3. Motion perception and ToM deficits, as measured by coherence thresholds and the Eyes Test, were observed in remitted schizophrenia patients and were highly correlated. Negative symptoms, but not paranoia, were related to the ToM deficit. In the investigated range, there was no correlation between IQ and ToM. This again indicates the deficit of the M pathway/dorsal stream system, which is related to ToM dysfunctions.

4. The ToM deficit was less severe in remitted patients than in patients with active clinical symptoms and was absent in unaffected biological relatives of schizophrenia patients. This suggests that ToM dysfunctions depend on the development of psychosis, even when it is in remission; a pure genetic vulnerability in unaffected, healthy relatives is not sufficient to induce ToM impairments, as measured by the Eyes Test.

6. General discussion

Contemporary research indicated that multiple interacting memory systems exist in the brain. The basic distinction refers to implicit (procedural) and explicit (declarative) memory (Gabrieli, 1998). Explicit (overt) memory refers to conscious recollection of facts and events, whereas the contents of implicit (covert) memory are inaccessible for conscious information processing. On the other hand, working memory consists of the central executive (or supervisory attentional system) and two "slave systems", one of which is specialized for the short-term, active maintenance of language materials (phonological loop), and the other serves the active maintenance of visual information (visuospatial sketchpad). The central executive participates in the attentional control and manipulation of information maintained in the "slave systems" in order to achieve encoding and retrieval of explicit memory traces, abstraction and planning, evaluation/decision-making, initiation, inhibition of immediate responses in pursuit of a long-term goal, and self-monitoring (Baddeley, 2003). Learning lists of words or face-name associations are classic examples for explicit memory, whereas acquisition of sensory-motor skills and stimulus-response patterns (multi-step "tower-type" tests, mirror drawing, and pursuit rotor tasks) are subjects to implicit memory. The medio-temporal (hippocampal) and diencephalic structures are candidate neuronal substrates for explicit memory, whereas implicit processes are mediated by sensory neocortex, basal ganglia, and cerebellum. Working memory is related to the interaction of lateral prefrontal cortex and posterior neocortex. Novel evidence suggests that these memory systems are organized in a tightly interactive and competitive manner (Baddeley, 2003).

Most of the studies on memory processes in schizophrenia have demonstrated impaired explicit and relatively preserved implicit functions such as repetition priming and procedural skill learning (McKenna et al., 1990; Goldberg et al., 1993; Brébion et al., 1997). Deficient explicit memory has also been shown in healthy relatives of schizophrenia patients, which may be related to subtle hippocampal pathology, a putative endophenotype of schizophrenia (Seidman et al., 2003). Dysfunctions in verbal memory are closely related to the social impairment of the patients (Green, 1996). In this thesis, additional evidence is provided that implicit prototype and probabilistic learning are preserved in schizophrenia, which further supports the notion that implicit processes are relatively spared. Verbal recall of words was impaired in siblings of schizophrenia and bipolar patients, which may point to the pathology of prefronto-hippocampal connections as an endophenotype of these disorders.

When the VBM and related methods were developed, little was known about the functional organization of the visual system. Advances in visual neuroscience revealed that parallel M and P visual pathways exist, which originate in retinal ganglion cells and project to the primary visual cortex via the lateral geniculate nucleus. M pathways (transient channels) are sensitive for low luminance contrast, low spatial frequency, and rapid temporal changes of brief stimulus exposure, fast offset, and motion. In contrast, P pathways (sustained channels) prefer static stimuli with medium and high spatial frequency (fine details of objects) and colors (Livingstone and Hubel, 1988; Van Essen and Gallant, 1994). Despite a substantial overlap and interaction between M and P pathways even in primary visual cortex, M pathways give a strong input to cortical areas responsible for the analysis of motion and spatial location (dorsal occipito-parietal stream) and P pathways project to ventral occipito-temporal regions related to color perception and object recognition (Van Essen and Gallant, 1994).

Many aspects of visual dysfunctions in schizophrenia can be interpreted in the framework of M and P pathways (Schwartz et al., 2001). Although results are not straightforward, evidence suggests that in patients with schizophrenia and their unaffected biological relatives M pathways and their cortical recipients are more impaired than P pathways and the ventral visual stream. This may explain why target location VBM (M pathway function) is more affected that target identification VBM (P pathway function) in schizophrenia patients and their siblings (Green et al., 1994a,b, 1997; Cadenhead et al., 1998). M pathway/dorsal stream dysfunctions may explain problems with smooth pursuit eye movements, which imply that patients fail to track moving objects with an adequate speed of eye movements (Chen et al., 1999). The second main purpose of the thesis was to investigate the relationship between VBM deficits and higher-level cognitive dysfunctions in relatives of patients with schizophrenia and psychotic bipolar disorder.

According to Gottesman and Gould (2003), endophenotypes are associated with the illness, present in unaffected biological relatives at a higher rate than in the general population (heritable), can be detected in remitted patients (trait- rather than state-dependent), and co-segregate with the illness in affected families. Several studies indicated that working memory/ executive functions, sustained attention, sensory gating, smooth pursuit eye movements, verbal memory, and language production are potential endophenotypes of schizophrenia (for review, see Gottesman and Gould, 2003; Kéri and Janka, 2004). However, almost all of these cognitive dysfunctions are less powerful markers and can be reliably detected only in 20-30%

of unaffected relatives. Therefore, research for new markers is of special importance. In this thesis, we suggest that the impairment of the M pathway/dorsal stream system is a potential endophenotype of schizophrenia.

Until recently, the vast majority of information on visual system dysfunctions has derived from VBM and CPT studies. Butler et al. (2001) recorded steady-state evoked potentials over the occipital cortex of schizophrenia patients and normal controls and found lower responses for M pathway stimuli (low spatial frequency with low luminance contrast) in schizophrenia patients relative to controls. There was no significant difference for P pathway stimuli (high spatial frequency with isoluminant colors). During a perceptual closure task, Doniger et al. (2002) found reduced P1 event-related potential over the dorsal occipito-parietal cortex, while the ventral N1 component was spared. Doniger et al. (2002) concluded that the selective reduction of the P1 component is consistent with impaired M pathways in schizophrenia. Finally, using high temporal frequency stimuli during functional magnetic resonance imaging (fMRI) measurements, Braus et al. (2002) demonstrated abnormal activation in the dorsal stream of schizophrenia patients, which is consistent with previous psychophysical results (O'Donnel et al., 1996).

However, some cautionary notes must be made. First, it is important that not all studies were able to confirm the differential impairment of the M pathway/dorsal stream system (Slaghuis, 1998), which is influenced by psychometric task properties such as difficulty and variance. It is highly likely that in more severely affected patients, gross deficits in visual functions are present. Second, it is unclear whether the observed dysfunction is due to the pathology of precortical M pathways or to alterations confined to higher-level visual cortices. Third, it has been proposed that M pathways are over-active in schizophrenia. The signal of the mask during VBM is relayed by the over-active M pathways that severely disrupts target processing, leading to a deficient performance. The over-activity of M pathways was supported by studies demonstrating abnormally low contrast threshold (high sensitivity) for temporally modulated low spatial frequency gratings (Antal et al., 1998). Bedwell et al. (2003) demonstrated that color red failed to inhibit M pathways in relatives of schizophrenia patients, again pointing to the over-activity phenomenon. However, over-activity does not necessarily mean superior performance; a lack of efficient inhibition may lead to information overload, performance decline, and finally gross disorganization (Braff, 1993).

Given the matched decisional component, motion and form coherence thresholds provide a unique opportunity to investigate the neuronal correlates of static and dynamic stimulus processing. Braddick et al. (2000) used fMRI to compare brain activation during form and motion coherence measurements. Two cortical areas were identified that responded selectively to moving stimuli: V3a in the dorsal occipito-parietal junction and V5 in the middle/superior temporal cortex. As elements of the classically defined dorsal stream, these regions receive strong input from M pathways and participate in motion processing (Van Essen and Gallant, 1994). Consistently with our behavioral data, dorsal stream areas were under-activated in the Braus et al. (2002) study. The dorsal visual stream is functionally connected with the dorsolateral prefrontal cortex, which is responsible for selective attention and working memory/executive functions (Goldman-Rakic, 1994). Area V5 also is related to the superior temporal sulcus (STS), which is specialized for the processing of biological motion such as dynamic facial expression and other aspects of body language (Allison et al., 2000). The STS exhibits significant activity during ToM tasks, including the attribution of mental states on the basis of gaze (Calder et al., 2002). It is of particular interest that in autism, which is characterized by severe ToM impairments, motion coherence threshold is increased (Spencer et al., 2000). This might explain the strong correlation between motion perception and Eyes Test performance in our patients with schizophrenia. Functional neuroimaging studies suggest that multiple elements of the ToM network are affected in schizophrenia, including the dorsomedial prefrontal cortex, left lateral prefrontal cortex, and STS (Russell et al., 2000; Brunet et al., 2003).

The above described speculative synthesis suggests that the dorsal visual stream may be an interface between early-stage sensory processing, basic neurocognition (attention and working memory), and social cognition. Vidyasagar (1999) suggested that temporal changes processed by the M pathway/dorsal stream may activate and guide the attentional spotlight to external stimuli. Indeed, rapidly changing visual patterns elicit brain activation in the cascade of thalamus, V5, and lateral prefrontal cortex, which latter is well known from its role in attention and working memory (Braus et al., 2002). Social cognition may be a mediating factor between basic neurocognition and community reintegration, which is essential to define measurable parameters that should be targeted by effective pharmacotherapy and psychosocial rehabilitation.

ToM refers to a possibly unique human ability to attribute beliefs, intentions, and feelings to other persons. Recent research has demonstrated that ToM can be dissociated from

other cognitive functions and is related to a relatively specialized social cognitive network in the brain, including the medial prefrontal and cingulate cortex, posterior superior temporal cortex, and temporal pole (Gallagher and Frith, 2003). There are many types of tasks measuring ToM; some of them include interactive games, while others use verbal stories that require the attribution of mental states of protagonists, irony, and metaphor. Comic-strips of short stories with characters with different beliefs also are used. Finally, mental states can be read from faces and eyes expressions (Eyes Test, Baron-Cohen et al., 2001), which is related to wider areas of social cognitive impairments of schizophrenia patients, including perception of basic emotions and social cues, as well as severe dysfunctions in everyday social skills (Penn et al., 1997).

ToM has consistently been shown to be impaired in patients with schizophrenia, similarly to patients with autism-spectrum disorders (Baron-Cohen et al., 2001). In contrast to initial evidence (Frith and Corcoran, 1996), the deficit does not appear to be specific for paranoid delusions; rather, schizophrenia patients with negative symptoms and disorganized thinking and speech exhibit the most severe impairments (Drury et al., 1998; Sarfati and Hardy-Bayle, 1999). Although ToM dysfunctions correlate with other cognitive deficits, including working memory/executive functions and verbal abilities (Juhász et al., 2003), the relationship between ToM and visual impairments has not been elucidated yet. This was the third main purpose of the thesis; we confirmed the relationship with negative symptoms, but not with IQ or paranoia, and demonstrated an intriguing correlation with dorsal stream pathology (motion perception). ToM deficits seem to be trait markers and not endophenotypes.

7. Acknowledgements

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II. Kéri S, Kelemen O, Szekeres Gy, Bagóczky N, Erdélyi R, Benedek Gy, Janka Z. Kognitív készségek szkizofréniában: eredmények vizuális kategória-tanulási folyamatokból. *Magyar Pszichológiai Szemle* 2001; 56: 501-512.

III. Kéri S, Szendi I, Kelemen O, Benedek G, Janka Z. Remitted schizophrenia-spectrum patients with spared working memory show information processing abnormalities. *European Archives of Psychiatry and Clinical Neuroscience* 2001; 251: 60-65.

IV. Kéri S, Kelemen O, Benedek G, Janka Z. Different trait markers for schizophrenia and bipolar disorder: a neurocognitive approach. *Psychological Medicine* 2001; 31: 915-922.

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VI. Kelemen O, Erdélyi R, Pataki M, Kéri Sz, Benedek Gy, Janka Z. Theory of mind and motion perception in schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience,* under revision

VII. Kelemen O, Kéri S, Must A, Benedek G, Janka Z. No evidence for impaired „theory of mind" in unaffected first-degree relatives of schizophrenia patients. *Acta Psychiatrica Scandinavica*, in press