Cognitive and motor disorders in schizophrenia

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Received: 14.06.2012   Accepted: 22.08.2012   Published: 18.09.2012

Abstract

Schizophrenia still remains a serious chronic psychiatric disorder with a lifetime prevalence in the general population of 0.8-1.0%. This disease causes great human suffering for the patient himself and his family and forms a major challenge in terms of functional outcome and quality of life, and of societal costs. The schizophrenic syndrome encompasses positive, negative, cognitive and depressive symptoms. Delusions, hallucinations and formal thought disorder are classified as positive symptoms, while affective blunting, poverty of thought and speech, and apathy are listed as negative symptoms. The cognitive cluster refers to alterations in processing speed, attention, working memory, verbal and visual learning and memory, executive functions and social cognition. Psychomotor symptoms comprise disturbances in the planning, the programming, the execution and the monitoring of movements; at the clinical level these psychomotor changes are expressed in psychomotor poverty, catatonic symptoms, neurological soft signs and extrapyramidal symptoms.

Whereas since the development of neuroleptic medications in the fifties and sixties of the past century the positive symptoms have been a major focus of clinical and scientific attention, interest in the cognitive and motor symptoms has highly increased in the past 15 years. It has been established that these symptoms have a much stronger relationship with the functional outcome of the patients than positive symptoms, in terms of the level of daily activities, the vocational capacities, and the interpersonal and social functioning.

By a joint initiative of the National Institute of Mental Health, the Food and Drug Administration, the academic research centers and the pharmaceutical industry, called MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) a consensus test battery was developed in order to measure systematically the different types of cognitive disturbances. In each cognitive domain animal models and tests were developed for translational purpose. New molecular targets for treating these cognitive deficits were defined, such as: the nicotine receptor in the hippocampus, the dopamine receptor (D1) in the prefrontal cortex (PFC), the 5HT2a-receptor and the noradrenergic receptor in the prefrontal and the anterior cingulate cortex (ACC), and the histamine receptor (H3); research further focusses on glutamate enhancers, muscarinic agonists and GABA-A partial agonists. The effects of these numerous compounds are investigated in normal healthy volunteers and
schizophrenic patients using cognitive psychological tasks, electrophysiological methods, neuroimaging and genetics. An example of studies in our research group are the effects of antipsychotics on the amplitude of the Error Related Negativity (ERN), an event related potential generated in the ACC immediately after making an error. Finally the massive increase into social cognitive research in schizophrenia is summarized. This fast expanding scientific domain involves emotional processing, social perception and knowledge, attribution bias, and Theory of Mind (ToM) or mentalizing.

It is concluded that the actual research into cognitive and motor processes in schizophrenia aims at increasing the specificity of the dysfunctions in different cognitive domains, basal processes and underlying neural networks, and the sensitivity for the effects of new compounds. This knowledge favors our insight in the physiopathogenesis of schizophrenia as a neurodevelopmental disorder.

**Keywords:** schizophrenia, cognition, motor, cognitive enhancers, social cognition.

**INTRODUCTION**

Schizophrenia remains up to now one of the most serious and poorly understood psychiatric disorders with great human suffering for patients and their relatives, a poor functional outcome and a high societal cost. The condition, or rather this group of conditions (“Der Gruppe der Schizophrenien”) was first described by Eugen Bleuler in 1911 (1), after Kraepelin’s “dementia praecox”, a concept that appeared for the first time in the fourth edition of his textbook in 1893 (2).

Psychiatric disorders can roughly be divided following the “trias psychica, i.e. cognition, emotion (mood-affect) and behavior (conative functions). Whereas schizophrenia can be characterized as a form of psychosis which most striking features involve cognition, mania and melancholia are designated as disorders of affect, and antisocial personality disorder/psychopathy, as a behavioral disturbance.

Looking at the history of the nosological concept of schizophrenia and its treatment, it is remarkable that psychiatry has focused on psychological (psychoanalysis, family and systems theories and models) and even social explanations (anti- or critical psychiatry), and that since the discovery and worldwide use of antipsychotic medication the importance of the positive symptoms, i.e. delusions and hallucinations was highlighted. It is only since the early nineties that the cognitive nature of the disorder has been “re-discovered” and has been a main topic of scientific research. Indeed the development of cognitive and affective neurosciences has generated a large interest in the cognitive and motor symptoms of schizophrenia, and in the processes and the basic neurobiological mechanisms that are underlying these symptoms. An important finding was the relationship between these cognitive deficits and several domains of the functional outcome of the schizophrenic patient. This was a stimulus for the search for new interventions, as well pharmacotherapeutical as psychological (cognitive training and remediation; cognitive behavioral therapy) aimed at
improving the cognitive functioning of patients with subacute or chronic schizophrenia.

After a short overview of the symptomatology and classification, the epidemiology and course of the disease, and of the main etiopathogenetic factors, this article will mainly focus on the cognitive and motor disorders in schizophrenia, as potential new targets for treatment.

SYMPTOMATOLOGY AND CLASSIFICATIONS

Symptoms can be clustered into four categories, i.e. (a) positive, (b) negative, (c) cognitive and (d) affective. (a) Positive symptoms encompass hallucinations and delusions, and disorganized or catatonic behavior. Delusions are highly individual ideas or beliefs of which a person is firmly convinced and failed to be corrected by contradictory evidence (autoperformant or autodecretal character). Hallucinations are defined as sensory perceptions with a reality character without external source (perceptio sine perceptum); the most common type in schizophrenia are auditory hallucinations, mainly voices. (b) In the category of negative symptoms are listed: affective flattening, apathy, poverty of speech, social withdrawal, flattening of facial expression, loss of initiative and lack of spontaneity, and loss of self-care. (c) The domain of cognitive symptoms will be explored below. At the clinical level formal disturbances of normal thinking are present such as derailment (loosening of associations), tangentiality, incoherence, blocking of thinking (“Sperrung”), illogicality, circumstanceality, concretisms and neologisms, echolalia and difficulties in abstract thinking. (d) Finally, affective symptoms mainly concern depression and anxiety, guilt feelings and tension, although excitement symptoms - hostility and aggression- and (hypo)mania are also possible.

Current classification mostly follows the diagnostic criteria for schizophrenia listed in the Diagnostic and Statistical Manual of Mental Disorders (DSM IV-TR) of the American Psychiatric Organization (3). A frequent symptom consists of loss of insight in the disease (anosognosia), which has a negative impact on treatment compliance. In the large majority of patients the disease has severe repercussions on functional and vocational outcomes, with high societal costs. Even more important is the mental suffering for patients and their families; studies, also in Belgium revealed suicide rates from about 10 to 15 percent.

EPIDEMIOLOGY AND COURSE

The lifetime prevalence of schizophrenia is about 0.8 %, the incidence (number of new cases per year) 0.2 %. The incidence is higher in the city areas (opposed to rural areas) of the industrialized world. Schizophrenia is more prevalent in men than in women; in men the first symptoms mostly occur before age 25, in women the disease usually begins five years later. Positive symptoms are responding well to
treatment. Recurrence or relapse of positive symptoms are frequent in about 75% of the patients. A small proportion of patients display positive symptoms continuously. Although in 15% of the patients symptoms disappear quite fully, this does not mean that their social functioning has restored. Negative symptoms remain more stable during the course of the disease. The course of the disease is difficult to predict. After the first 5 to 10 years the state remains more or less stable in the majority of patients. It has to be stressed that in case of insufficient care the risk of social exclusion with homelessness, poverty and marginalization subsists.

ETIOPATHOGENESIS

In the past decades, schizophrenia has been more and more considered as a neurodevelopmental disorder in which genetic and early environmental factors play a critical role. Neurodegenerative theories already noted by Kraepelin and Alzheimer have not been finally confirmed. In the last decade more than 1000 reports have been published on the psychophysiological changes in schizophrenia (4): structural brain changes in grey and white matter and functional deficits showed by brain imaging and electrophysiological techniques. From a neurotransmission point of view, changes in mesolimbic and mesocortical dopaminergic systems have been considered as a major pathogenetic factor besides glutamatergic, GABA-ergic, and serotonergic alterations.

COGNITIVE AND MOTOR DYSFUNCTIONS

In 1994 Saykin et al. (5) published a paper in the Archives of General Psychiatry in which they indicated the cognitive domains in which first episode and previously treated patients performed below the normative level. It concerns attention-vigilance, abstraction-flexibility, verbal intelligence and language function, spatial organization, verbal memory and learning, visual memory, speeded visual motor processing and attention, and fine manual motor functions. Patients performed between -1 and -2.5 SD below that of control subjects. These findings were replicated many times since then. Overall a decrease of +/- 10 IQ-points was registered. In some studies a major cognitive decline was demonstrated. For instance Wilk C.M. et al. (6) used the Manual Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), a composite cognitive score analogous to the WAIS-IQ score, in order to compare schizophrenic patients (N=575) and normal controls (n=540). A major shift to the left (-30 to 40 points) can be observed in the patient group, indicating again the major cognitive loss that is implicated in the disease (7).

The renewed attention for the cognitive deficits in schizophrenia was strongly supported by the link with the functional outcome of the patients, that was observed by several research groups in the nineties and the early two thousands. For instance, already in 1996 Green et al. (8) established links between verbal
memory and overall outcome, vigilance and social skill acquisition, between executive functioning and community functioning and between social problem solving and negative symptoms.

Subsequent studies by Mueser and McGurk (9) showed that cognitive impairment is strongly related to functioning in profession, social interactions and independent living.

PSYCHOMOTOR SYMPTOMS AND OUTCOME

For an overview of the literature we refer to the review article of our group on psychomotor slowing in schizophrenia (10). In this paper we concluded to “evidence for an association between speed of psychomotor functioning and social, clinical and functional outcome”. Cancro et al. (11) found reaction times to be predictive of clinical outcome 3 years later. Processing-speed tasks such as the Symbol Digit Substitution Task, Trail Making Task and the Stroop have been associated with better employment outcomes and quality of life and hospital inpatient status.

MATRICS: MEASUREMENT AND TREATMENT RESEARCH TO IMPROVE COGNITION IN SCHIZOPHRENA (12)

An important step forwards in the research on cognition in schizophrenia was made by the MATRICS-initiative (Measurement And Treatment Research To Improve Cognition in Schizophrenia) (12). In 2002 this joined initiative of the National Institute of Mental Health (NIMH), in collaboration with the academia, the pharmaceutical industry and the Food and Drug Administration (FDA) aimed at creating a standardized cognitive battery for use in clinical trials and facilitating the paths to FDA approval of new “cognitive enhancing” compounds. It was established that current psychopharmacological treatments for schizophrenia are mainly targeting positive symptoms, and have only very limited effects on negative and cognitive symptoms. Current therapeutics show major limitations: Only 1 patient in 5 is sufficiently recovered to work; 90% of patients with a first episode will go on to relapse; and medicines are of limited effects in 25-30%.

The overall impression consists of a ceiling effect with the available drugs. It is argued that the psychopharmacology of the future will have to dissect the DSM-disorders in dimensions in order to reach new clinical targets that are more proximate to pathophysiology. New drugs and new molecules aimed at these targets should demonstrate clinical effects on currently untreated dimensions of psychopathology. Previous approach in psychopharmacological research demonstrated broad classes such as anxiety, depression and psychosis; current approach is focused on specific diseases/syndromes, specific symptoms or symptom clusters and non-specific symptoms.

MATRICS underlined the public health importance of cognition in schizophrenia, indicating the poor correlation with functional outcome of
delusions (-0.08), hallucinations (-0.09) and thought disorder (-0.22*); in contrast the correlation between cognitive impairment (immediate verbal memory) and functional outcome is highly significant (r= -0.40**). The NIMH has identified obstacles that are likely to interfere with the development of pharmacological agents for treating cognition in schizophrenia. These include: (1) a lack of consensus as to how cognition in schizophrenia should be measured; (2) deferring opinions as to the pharmacological approaches that are most promising; (3) challenges in clinical trial design; (4) concerns in the pharmaceutical industry regarding the US FDA approaches to drug approval for this indication; and (5) issues in developing a research infrastructure that can carry out clinical trials for promising drugs.

The MATRICS program aimed bringing together representatives of academia, industry and government in a consensus process for addressing all of these obstacles.

Consequently MATRICS identified cognitive targets in schizophrenia, a consensus test battery for measuring the deficits in these cognitive domains, and lead compounds of potential utility in human cognition augmentation trials in general, and in schizophrenia specifically.

In MATRICS it was concluded that the following 7 cognitive domains could be identified as separable and grossly independent in order to target cognitive deficits in schizophrenia.

1. Attention/vigilance: answering correctly on a series of fast presented stimuli. Example: being able to read a book or watch a movie.
2. Working memory: maintaining and manipulating information in short periods of time (approximately 5-20 sec.). Example: remembering a telephone number that you just obtained.
3. Verbal learning and memory: remembering verbal information over longer periods of time (minutes to years). Example: remembering a given shopping list.
4. Visual learning and memory: remembering visual information over longer periods of time (minutes to years). Example: remembering where you have stocked some object.
5. Reasoning and problem solving: the capacity to apply effectively adequate strategies. Example: arriving on time at work even if the travel scheme of the busses has been changed.
6. Processing speed: processing information and quickly responding without errors. Example: using a touch-screen computer to serve clients in a fast-food restaurant.
7. Social cognition: effectively processing and remembering social information such as facial expressions and emotions, the meaning of social interactions. Example: remembering the name and the face of someone you have
met; understanding that someone is not angry with you.

Our research group (10) argued that the dimension of processing speed should be separated in two independent dimensions: processing speed and psychomotor functioning. Besides reduction in processing speed, psychomotor slowing is a clinically observable feature in schizophrenia. For an overview see (10). Apart from psychomotor slowing patients may exhibit catatonic symptoms and neurological soft signs (NSS). Catatonic symptoms are specific motor abnormalities such as stereotypy, stupor or mutism, that are associated with other psychiatric disorders. NSS include deficits in motor coordination, motor sequencing and sensory integration. The relationships between these various domains of psychomotor symptoms is currently under investigation in a longitudinal study, supported by IWT-Flanders (13).

SUBJECTIVE EXPERIENCE OF COGNITIVE DYSFUNCTIONS

Using the Frankfurt Complaint Questionnaire, Moritz S. et al. (14) demonstrated that schizophrenic patients reported significantly more cognitive and perceptual problems than healthy subjects. These complaints can take different forms. Patients can suffer from: loss of control over their own thinking processes, f.i. “I can’t determine what I will think about”. Sometimes difficulties in simple/complex perception are more pronounced. Language problems can occur: f.i. “While speaking, the word I intended to use, is lacking”. Some patients complain of thinking difficulties: f.i. “It demands a continuous effort to order/structure my thoughts”. Also memory or motility can be affected. Patients can experience lack of automatisation: f.i. “The daily routine doesn’t function anymore as usual, I have to reflect on every step”. Finally subjective complaints concern anhedonia/anxiety and sensory overstimulation.

THE MATRICS CONSENSUS COGNITIVE BATTERY; TRANSLATIONAL RESEARCH

A ranking was made of the most important test qualities for selecting and composing a test battery that could be widely used in the search for new cognitive enhancing compounds. Tests should demonstrate a high test–retest reliability, a good coverage of individual cognitive constructs; comparable alternative forms; a clear relationship to functional outcome; a strong internal consistency of individual scales; well-established norms for the general population; a highly interpretable overall summary score; a clear relationship to known neural systems and to clinical symptoms. Finally the following test battery was agreed upon, of which the total estimated duration is about one hour:
Furthermore also a battery of animal models/test was proposed, covering the seven cognitive domains:

**Table 2. Cognitive domains affected in schizophrenia (MATRICS Proposed battery): animal models and clinical battery (http://www.matrics.ucla.edu/)**
Using these animal models and tests, the effects of various neuropharmacological interventions on the 5 Choice Serial Reaction Time Task (5CSRTT) were investigated (15). It was found that the following compounds enhanced the accuracy of the 5CSRTT: intra-mPFC (medial prefrontal cortex) D1 agonists, intra-mPFC 5HT2A antagonists, intra-mPFC 5HT1A agonists, systemic nicotine, systemic physostigmine, systemic alpha-1 agonists and systemic D2 antagonists in mPFC lesioned rats.

On the contrary the following compounds impaired the accuracy of the 5CSRTT: intra-mPFC D1 antagonists, intra-mPFC scopolamine, systemic D2 antagonists, systemic MK-801, systemic NR2B NMDA antagonists, cortical acetylcholine loss and cortical noradrenalin loss (under certain conditions).

NEW MOLECULAR TARGETS AND NEW PUTATIVE DRUGS

Based on this translational type of research putative molecular targets for treating cognition in schizophrenia were identified: the nicotine receptor in hippocampus, the dopamine receptor D1 in PFC, 5HT2a receptor in PFC/ACC, the noradrenergic receptor in PFC/ACC, the glutamatergic enhancers, the muscarinic agonists and the H3 histamine antagonists. For an extensive overview, see Table 3.

### Table 3. Overview of molecular targets for treating cognition in schizophrenia

<table>
<thead>
<tr>
<th>Molecular Target</th>
<th>Example Compound</th>
<th>Clinical Evidence</th>
</tr>
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<tbody>
<tr>
<td>D1 agonists&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Dihydrexidine</td>
<td>Positive proof-of-concept trials</td>
</tr>
<tr>
<td>D4 antagonists</td>
<td>Sonepiprazole</td>
<td>Ineffective in acute schizophrenia</td>
</tr>
<tr>
<td>D&lt;sub&gt;2&lt;/sub&gt; agonists</td>
<td>A-412997</td>
<td>n/a</td>
</tr>
<tr>
<td>COMT inhibitors</td>
<td>Tolcapone</td>
<td>Improved cognition in Parkinson’s disease</td>
</tr>
<tr>
<td>5-HT&lt;sup&gt;2A&lt;/sup&gt; antagonists</td>
<td>M100907</td>
<td>Modest efficacy in acute schizophrenia</td>
</tr>
<tr>
<td>5-HT&lt;sup&gt;1A&lt;/sup&gt; antagonists</td>
<td>Tandosprone</td>
<td>Mixed results</td>
</tr>
<tr>
<td>5-HT&lt;sup&gt;1A&lt;/sup&gt; antagonists</td>
<td>WAY106635</td>
<td>n/a</td>
</tr>
<tr>
<td>5-HT&lt;sup&gt;4&lt;/sup&gt; antagonists</td>
<td>Tegaserod</td>
<td>Recently withdrawn from market in IBS&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;X&lt;/sub&gt; antagonists</td>
<td>SB-271046</td>
<td>n/a</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;7&lt;/sub&gt; agonists</td>
<td>No selective ligands</td>
<td>Multiple trials, mixed results</td>
</tr>
<tr>
<td>Cholinesterase inhibitors</td>
<td>Donepezil</td>
<td>Positive proof-of-concept trials</td>
</tr>
<tr>
<td>Nicotinic α&lt;sub&gt;2&lt;/sub&gt; agonists</td>
<td>DMXB-A</td>
<td>n/a</td>
</tr>
<tr>
<td>Nicotinic α&lt;sub&gt;β&lt;/sub&gt; agonists</td>
<td>RJR2403</td>
<td>Positive effects with nonselective agonists</td>
</tr>
<tr>
<td>M&lt;sub&gt;1&lt;/sub&gt; agonists</td>
<td>NDMC (nonselective)</td>
<td>Positive proof-of-concept trials</td>
</tr>
<tr>
<td>M&lt;sub&gt;4&lt;/sub&gt; antagonists</td>
<td>No selective ligands</td>
<td>Mixed proof-of-concept trials</td>
</tr>
<tr>
<td>M&lt;sub&gt;2&lt;/sub&gt; antagonists</td>
<td>No selective ligands</td>
<td>Positive proof-of-concept trial reported</td>
</tr>
<tr>
<td>NMDA enhancers</td>
<td>Glycine</td>
<td>Positive small trials</td>
</tr>
<tr>
<td>GlyT inhibitors</td>
<td>Org-24598</td>
<td>Positive proof-of-concept trials</td>
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<tr>
<td>Ampakines</td>
<td>CX-516</td>
<td>Mixed proof-of-concept trials</td>
</tr>
<tr>
<td>mGluR2/3 agonists</td>
<td>Unknown</td>
<td>Positive proof-of-concept trial reported</td>
</tr>
<tr>
<td>mGluR5 agonists</td>
<td>CDPPB</td>
<td>Positive proof-of-concept trials</td>
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<tr>
<td>α&lt;sub&gt;2&lt;/sub&gt;-adrenergic</td>
<td>Guanfacine</td>
<td>Positive small trials</td>
</tr>
<tr>
<td>antagonists</td>
<td>TPA023</td>
<td>Single positive proof-of-concept trial</td>
</tr>
<tr>
<td>GABA&lt;sub&gt;A&lt;/sub&gt; (α&lt;sub&gt;2&lt;/sub&gt;)</td>
<td>L-655708</td>
<td>n/a</td>
</tr>
<tr>
<td>GABA&lt;sub&gt;A&lt;/sub&gt; (α&lt;sub&gt;4&lt;/sub&gt;)</td>
<td>No selective ligands</td>
<td>n/a</td>
</tr>
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</table>

AMPAKINES?

In our research group at the Radboud University of Nijmegen the effects of the ampakine Farampator 1-
(benzfurazam-5-ylcarbonyl) piperidine were investigated on memory and information processing in healthy elderly volunteers. Positive results were found in short term memory and the continuous trail making test. At this moment, no results in patients suffering from schizophrenia are available (17).

SOCIAL COGNITION

Recently, cognitive neuropsychiatry has demonstrated growing interest in deficits in social cognition in different psychiatric disorders such as schizophrenia, autism spectrum disorders, dementias (frontal temporal dementia and Alzheimer), antisocial personality disorder, bipolar disorder and normal ageing. “Social cognition has become a high priority area in schizophrenia” (18). Social cognition refers to the ability to infer one’s own and other persons’ mental states, i.e. the mental operations that underlie social interactions, including perceiving, interpreting and generating responses to the intentions, dispositions and behaviors of others. Social cognitive research in schizophrenia encompasses the following 5 domains (18):

1. Theory of Mind (ToM) involving the ability to infer intentions, dispositions and beliefs of others.
2. Social perception, referring to one’s ability to identify social roles, societal rules and social context.
3. Social knowledge, meaning the awareness of the roles, rules, and goals that characterize social situations and guide social interactions.
4. Attributional bias or style, reflecting how people typically infer the causes of particular positive and negative events.
5. Emotional processing, i.e. the perceiving and using of emotions.

The study of social cognitive processes and deficits in schizophrenic patients may be helpful to understand the pathogenesis of clinical symptoms and the (poor) functional outcome of the disease, and has become a target for psychological (psychotherapeutic and training/education) interventions and possibly new psychopharmacological strategies.

An interesting development consists of building bridges between the social cognitive constructs in schizophrenic patients and the social cognitive domains that are emerging from social neuroscience in non-clinical samples. By example, CNTRICS (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia) (19) identified 5 constructs in the social-emotional pathway that are overlapping with the domains mentioned above: (1) acquisition of social-affective values and responses, (2) recognizing and responding to social-affective stimuli, (3) “embodied” simulation or low-level mental state inference, (4) high-level mental state/trait inference, and (5) context-sensitive regulation.

Regarding schizophrenia as a neurodevelopmental disorder, with possible cognitive, emotional, motor and
behavioral changes early in life, it is especially interesting to investigate the ontogeny of ToM in children. It is unclear whether and how the development of ToM in subjects that will suffer from schizophrenia is different from normal children and from children with autism spectrum disorders; in these children ToM deficits are present at a very early age. Baron-Cohen (20) has proposed an ontogenic model of ToM maturation based on an evolutionary concept. In this model, very early in development, children pay attention to eye-like stimuli. At about 18 months, the human child is able to associate “seeing” with “knowing”, and to engage in pretend play. An important milestone is the capacity of shared attention, that seems to be a social skill that is unique to great apes and humans. Shared attention is more than simply looking at the same thing that another person is looking at; it adds the qualification that the two persons know that the other is looking at the same object: this becomes obvious by pointing as a sign of triadic interaction. Further stages of ToM development include understanding false beliefs and metaphors, irony, and faux-pas.

The concept of shared attention as developmental link between “seeing” and its determination by eye movements and “knowing” is particularly interesting in the light of the well-established disturbances in eye movements in schizophrenia: i.e. deficits in smooth pursuit eye movements (SPEM) are one of the most robust neuropsychological trait markers in this disease.

SUMMARY AND CONCLUSIONS

In search of a better understanding of the clinical syndrome of schizophrenia and its etiopathogenesis, the study of cognitive and motor processes underlying the different psychopathological phenomena of the disease, has highly increased during the last decade because of their relationship with the functional outcome of the patients. Collaborative efforts in programs such as MATRICS and CNTRICS have defined the altered cognitive domains, a consensus test battery and putative animal models and tests for each domain. Research into new compounds with (social) cognitive enhancing properties is ongoing, targeting a variety of CNS receptors and neurotransmission pathways. Actually no direct clinical application has resulted from this research.
LIST OF REFERENCES