Neurophysiological and neuropsychological assessment of recent-onset schizophrenia
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General introduction
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Pathophysiological mechanisms underlying disturbed brain function in schizophrenia

Schizophrenia is a relatively common disorder. Patients with schizophrenia can show deficits in almost all human mental activity (Andreasen, 1999). The prevalence in the Netherlands between the ages of 18-65 years is estimated at 6-7.5 per 1000 (Hodiamont, 1986). The total number of subjects with schizophrenia is estimated at approximately 100,000. Therefore, the costs in human suffering and medical expenses are large.

Schizophrenia is a disease of the brain. However, it is easier to make this assertion than to document any actual deviations in brain physiology. Since the illness represents a disturbance in some, but not all, brain functions, it is reasonable to suppose that specific areas or neural circuits of the brain are involved and that the manifestations of schizophrenia must necessarily involve altered processing of physiological information; this altered processing would, in turn, be dependent on disturbances of cytoarchitectural, biochemical, or electrophysiological properties of the neural systems.

Throughout most of this century, examination of postmortem brain tissue has been the principal source of data with relevance to the neuroanatomy of schizophrenia. Early reference to schizophrenia as "the graveyard of neuropathology" was not because of a lack of neuropathological findings, but rather because of the lack of a discernible pattern in the frequently observed pathological findings and the possibility that deviations were either artifactual in nature or were a consequence, rather than a cause, of the disease. Moreover, the widespread use of neuroleptic drugs in the treatment of schizophrenia introduced additional artifacts in the investigation of brain pathophysiology. Finally, knowledge of brain-behavioral relations was not sufficiently detailed to guide neuropathological inquiry during much of this century (Kaplan and Sadock, 2000).

Although no discernible pattern has been found yet in brain structure abnormalities with postmortem research, some brain function abnormalities are highly replicable in schizophrenic patients. Techniques of assessing brain function such as neurophysiological and neuropsychological measurements generally show disturbed functioning of the brain. Neurophysiological studies may provide insight into the pathophysiology of central nervous system disorders. Neuropsychological tests provide an indication of cognitive functions like memory and attention. Two neurophysiological techniques, Event-Related Potentials (ERPs) and eye movement recordings have been
reported to yield abnormal results in schizophrenic patients in previous studies. In addition, schizophrenic patients show reduced performance compared to intelligence and age matched healthy control subjects on a wide range of neuropsychological tests.

Research has indicated that performance on certain neuropsychological tests diminishes with focal brain lesions. By linking test results obtained by eye movement and ERP studies to results of a comprehensive neuropsychological test battery, it may be possible to gain more insight into the neuro-anatomical substrate of diminished performance on neurophysiological tests in schizophrenic patients (Nieman et al, 1999). Thus, the relationships between neuropsychological features and findings from eye movement and ERP studies may be valuable to investigate pathophysiological mechanisms underlying abnormal brain function in schizophrenia. Understanding these mechanisms is the first step in the clarification of the enigmatic etiology and pathophysiology of schizophrenia.

Eye movements
Eye movements are studied in schizophrenia because abnormalities may reflect CNS activity and circuitry that are relevant to the neurobiology of schizophrenia (Hutton and Kennard, 1998a). Reduced performance on the antisaccade and visual scan task have been reported in schizophrenic patients (O'Driscol et al, 1999; Matsue et al, 1994; Hutton et al, 1998a,b; Blackwood et al, 1991; Nieman et al, 2000).

Saccades are fast eye jumps that are executed to bring the object of interest onto the fovea. Visually guided (reflexive) saccades are elicited by a suddenly appearing visual target that captures attention and triggers a saccade to the target. In the antisaccade task, subjects are requested to inhibit a reflexive saccade to a suddenly appearing visual target and to look in the opposite direction at an equal distance of the central fixation point (Crevits et al, 2000). Patients with schizophrenia show reduced performance on eye movement tasks that require cognitive control like the antisaccade task (Hutton et al, 1998b; Matsue et al, 1994; Allen et al, 1996; Crawford et al 1995, 1996; Ross et al, 1998). Contrary to antisaccades, reflexive saccades that do not require cognitive control are normal in patients with schizophrenia (Levin et al, 1982; Yee et al, 1987). Visual scanning is an eye movement task that contains both cognitive and reflexive components. If subjects are requested to scan a picture freely, the eyes are initially drawn reflexively to points of interest, indicating the allocation of attention to the object (Norton and Stark, 1971). Subsequently, subjects may
cognitively implement a scanning strategy to gather additional information about the scene. The eye movement recording protocol used in this thesis included an antisaccade and a visual scanning task.

**Event-related potentials**
An ERP is a derivative of the electroencephalogram (EEG) and it consists of voltage fluctuations measured on the skull. These voltage fluctuations represent neural activity in the brain in response to sensory input. An ERP is obtained by averaging trials of EEG that have the same duration and that are recorded after application of the same stimulus. By means of this procedure, an ERP is profiled with a number of positive (P) and negative (N) components which can be classified in early, intermediate and late components. The early components have a latency shorter than 50 msec and are called evoked potentials (EPs). They represent the anatomically specific events in the relay of sensory information to the cortex (Grebb et al. 1986). The latency of the intermediate potential components lies between 50 and 150 msec. The intermediate components are relatively sensitive to fluctuations in attention. The latency of late potential components is longer than 200 msec and include the P300 (P3) that occurs 300 msec after task-relevant, unexpected and infrequent stimuli. P3 latency and amplitude vary strongly as a function of experimental manipulations that influence cognitive functions like attention.

The ERP research in schizophrenia has yielded three relatively consistent findings (Grebb et al. 1986). Firstly, amplitude of the early components tends to be increased in amplitude (Callaway and Naghdi, 1981; Kaplan et al. 1994). Secondly, the intermediate components are reduced in amplitude with most stimulus paradigms. Thirdly, the late components, notably the P3, are reduced in amplitude as well (Grebb et al. 1986). In some studies (Pfefferbaum et al. 1984; Blackwood et al. 1994; Souza et al. 1995) a prolonged latency of the P3 has been found. In this thesis, research was focused on the P300 because this ERP component yields the most replicable abnormal results in schizophrenic patients.

**Neuropsychological tests**
Cognitive abnormalities reported in schizophrenia include dysfunctions in working memory, attention, semantic memory retrieval, goal directed problem solving and motor speed (Grant and Adams, 1996). Working memory is fundamental to the human
ability to reason and make decisions that rely on remembered contextual information and is thought to be mediated mainly by the dorsolateral prefrontal cortex (Beardsley, 1997). Furthermore, working memory plays an important role in the inhibition of unwanted reflexive responses (Muri et al, 1998). Attentional dysfunctions appear to be a "trait" marker for schizophrenia, since they are also apparent in symptom free patients (Nuechterlein et al, 1986) and in children at risk of schizophrenia (Nuechterlein, 1983). In the present thesis, patients were assessed with a comprehensive neuropsychological test battery that includes the domain of attention, memory, executive function and motor speed. With this test battery a relatively complete picture of neuropsychological functioning of the patient can be obtained (Nieman et al, 1998). Which cognitive function is mostly drawn on when performing a scanning task, antisaccade task, and ERP task is uncertain since correlations between these tasks and a comprehensive neuropsychological test battery are yet relatively unexplored.

The heterogeneity of schizophrenic symptomatology
Symptomatology of this complex and serious disorder includes hallucinations, delusions, anhedonia, poverty of speech, social isolation and thought disorder (Costello et al, 1993).

An example of a disease history of a patient with schizophrenia
Simon is 17 and attends high-school. He feels uncomfortable with other people, he prefers to be alone. His interests become more and more focused on religion. He thinks that his development is part of an unknown and irrevocable higher plan. He thinks his mission from God is to save people and he gives 200 dollar to a homeless person. He skips school, continuously withdraws to his room and disappears from time to time for days. His family calls in the help of the family doctor who refers him to a clinic. After antipsychotic medication the delusion that he must save the world fades, he starts realizing slowly that what he thought may not have been true. Moments at which he realizes that he may be suffering from a severe mental disorder, he feels very depressed. After ten weeks Simon returns home. He is doing all right for some time until he feels he no longer needs antipsychotic medication. Delusions return and illness-insight disappears. A second hospitalization takes place, this time with a risk for suicide. It takes longer before the psychotic symptoms fade and the negative symptoms are more severe than after the first psychosis.
Although controversial, accumulating evidence suggests that schizophrenia may be a heterogeneous set of syndromes rather than a single disease entity (Johnstone and Frith, 1996). To distinguish between schizophrenic subtypes, patients have been categorized in positive (thought disorder, delusions, hallucinations and bizarre behavior) and negative (blunted affect, anhedonia, avolition, alogia) symptom categories (Strauss, 1978; Crow et al. 1986; Andreasen and Olsen, 1982). The positive symptoms are the psychopathological features that are present but should not be, such as delusions and hallucinations. The negative symptoms are those features that are not present but should be, resulting in for example lack of initiative and apathy. Initial investigations supported this distinction by demonstrating that patients with predominant negative symptoms tend to have worse prognosis, poorer premorbid function and more cognitive deficits than those primarily displaying positive symptoms (Andreasen and Olsen, 1982). However, subsequent research using the statistical technique of Principal Component Analysis indicated that the positive-negative dichotomy is inadequate (Arndt et al., 1991; Liddle, 1987). Rather, schizophrenic symptoms tend to fall along three dimensions, comprising positive, negative and disorganization symptoms. Disorganization symptoms include conceptual disorganization and difficulty in abstract thinking. The three clusters of symptoms (syndromes) should not be regarded as mutually exclusive but rather as semi-independent dimensions, possibly reflecting differential underlying neurophysiological processes (Liddle and Barnes, 1990; Van der Does et al., 1993). Accordingly, attempts have been made to identify clinical correlates of each of these symptom clusters. Indeed, there are suggestions that the three symptom dimensions have specific cerebral correlates, such as structural and functional abnormalities in multiple brain regions (Aderibidge and Gurje, 1996; Kaplan et al., 1993; Mozley et al., 1994; Schroder et al., 1995). Yet, relatively little is certain concerning neurophysiological and neuropsychological correlates of the three factors.

Previous research demonstrated an association between cognitive deficits and negative symptoms whereas impairment typically appeared unrelated to positive symptom severity (e.g. Buchanan et al., 1994; Perlick et al., 1992). However, these symptoms subsumed disorganization symptoms within measures of positive symptoms, thereby obscuring any potential relationship between disorganization symptoms and neuropsychological impairment. More recent research has addressed this shortcoming. Van der Does et al. (1993) found disorganization symptoms to be correlated with a
poorer performance on neuropsychological tests indicative of selective attention whereas positive and negative symptoms did not correlate with any of the neuropsychological tests. In this thesis, the negative, positive and disorganization symptom dimensions are investigated with neurophysiological assessments to gain more insight into their biological substrates.

Neurophysiological correlates of symptom dimensions of schizophrenia have also been investigated. Biological marker research has indicated that negative symptoms may be related to prefrontal dysfunction and positive symptoms to temporo-limbic dysfunctions. However, across studies, conflicting findings have been demonstrated. In addition, most studies have been performed in an older, more chronic population of schizophrenic patients than the group that has been investigated in the studies of the present thesis. In older schizophrenic subjects, medication and hospitalization effects may influence results to a greater extend than in young, recent-onset schizophrenic patients. Investigating the biological substrate of symptom dimensions in schizophrenia is important because clarification of the possibly differential biological substrate of the symptom dimensions could play a role in the development of more specific, and therefore more adequate treatments of this serious disorder.

Antipsychotic medication

Antipsychotic medication can reduce positive symptoms. However it can not cure schizophrenia. If medication is discontinued, psychotic symptoms may return. Medication that effectively reduces negative and disorganization symptoms is not available. The exact mechanism of the favorable effects of antipsychotic medication on positive symptoms is unclear. Blockade of the dopamine receptors is probably implicated because most antipsychotic medications block these receptors. However, although antipsychotics are fully effective in blocking dopamine receptors within hours after they are administered, their antipsychotic activity requires several weeks to become apparent (Bear et al., 1996).

Antipsychotic medication was introduced in the fifties. These classic antipsychotic drugs, like chlorpromazine and haloperidol, display a high affinity for the dopamine D2 receptor and can induce motoric disturbances, i.e., tardive dyskinesia and extrapiramidal side effects such as tremors. More recent atypical antipsychotic medication, e.g., olanzapine and risperidone show, besides affinity for dopamine receptors, affinity for several other receptors, especially the serotonergic (5-HT)
receptor. These two atypical antipsychotics have a differential receptor binding profile. For example risperidone displays affinity for the adrenergic alpha2 receptor whereas olanzapine does not.

Antipsychotic medication may influence aspects of performance on neurophysiological tests. The effect of antipsychotic medication on e.g. reflexive saccades, antisaccades and the P300 is inconclusive. Studies in which performance of young antipsychotic naive schizophrenic patients was investigated, have shown that performance on these tests in young patients is not determined entirely by antipsychotic medication. For example, antisaccade error rate was also increased in patients without current and previous antipsychotic medication (Crawford et al, 1995; Hutton et al, 1998b). P300 amplitude tends to ameliorate slightly with antipsychotic medication but not to normal levels. In this thesis, the majority of the patients was treated with olanzapine or risperidone, making the patient group more homogeneous. Differential effects of olanzapine and risperidone were investigated to gain more insight into the effect of antipsychotic medication on neurophysiological assessments.

Aim and outline of the study
Considering the above, the aim of the study is:
To investigate the neurobiological substrate of disturbed brain function in recent-onset schizophrenia with neurophysiological and neuropsychological assessments.

It can be divided into the following parts:
a) To investigate differential pathophysiological mechanisms underlying three symptom dimensions in schizophrenia
b) To investigate the effects of differential receptor blockade of risperidone and olanzapine on neurophysiological test results

In chapter 2, the neurobiological substrate of schizophrenia is investigated with the antisaccade test. Eye movement disorders in schizophrenia have frequently been reported. A review was recently published in Neurology in which the authors stated that relationships with symptomatology, medication and neuropsychological tests have hardly been explored and that most recording methods of eye movements used in the past, for example the electro-oculogram (EOG) method, are not reliable (Hutton and Kennard, 1998a). In the present study, eye movements are recorded using the double
magnetic induction method with a high temporal and spatial resolution. The first aim of the present study was to elucidate pathophysiologic mechanisms involved in abnormal antisaccade task performance in schizophrenia, by investigating a possible relationship between antisaccade task performance and neuropsychological tests and symptomatology in a group of young patients with recent-onset schizophrenia. The second aim was to compare the effects of olanzapine and risperidone on antisaccades and reflexive saccades in young schizophrenic patients.

Chapter 3 deals with another part of the eye movement recording protocol: visual scan patterns. Abnormal visual scan patterns have often been reported in schizophrenic patients (Gaebel et al, 1987; Philips and David, 1998). However, most visual scan studies were performed in older, more chronic patients and relationships with a comprehensive neuropsychological test battery were not investigated as yet. The aim of this study was to gain insight into the nature of visual scan deficits in recent-onset schizophrenia by investigating relationships among visual scan patterns, neuropsychological performance and symptomatology in young schizophrenic patients with a relatively short exposure to antipsychotic medication. The relationship between scan patterns and interpretation was also investigated. To our knowledge, this relationship has not been investigated extensively as yet.

Amplitude reduction of the P300 ERP component is one of the most replicable biological abnormalities in schizophrenia (Ford, 1999; Higashima et al, 1998). However, despite the large volume of work on the P300 it has been difficult to elaborate its specific functional role, or to characterize the underlying neural machinery (Pineda et al, 1993). A hypothesis is formed in chapter 4 about the role of the nucleus reticularis of the thalamus in P300 amplitude reduction in schizophrenia.

The underlying neural machinery of P300 amplitude reduction is investigated further in chapter 5, with the aim to gain insight into pathophysiological mechanisms underlying abnormal brain function in schizophrenia. Neuropsychological test results and symptomatology are linked with the P300, in a homogeneous group of young recent-onset schizophrenic patients. The P300 has usually been recorded in one session. Recording the P300 in two consecutive sessions with an intermission of five minutes, may give insight into time dependent changes in P300 amplitude and latency. Negative symptoms have been found to relate to a time dependent decrease in performance on neuropsychological tests (Everett et al, 1989). We investigated if negative symptomatology is also related to a time dependent decrease in P300
amplitude. Furthermore, differential effects of olanzapine and risperidone on the P300 were investigated.

The core symptoms of schizophrenia are subjectively experienced alterations in perception, cognition and emotion. Schizophrenia is diagnosed mainly by means of interviews with the patient. Relating biological markers like the P300 to subjective experience in schizophrenia may increase the interpretability of P300 abnormalities and may validate the assessment of subjective experience in schizophrenic patients. Data on the relationship between subjective experiences of schizophrenic patients and a biological marker like the P300 are scarce. Chapter 6 aims to investigate the relationship between the P300 and subjective experience. In chapter 7, the results described in chapter 2 through 6 are combined in one model of neurobiological dysfunctions underlying schizophrenic pathology.

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