Neurophysiological and neuropsychological assessment of recent-onset schizophrenia
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Chapter 7

General discussion
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In the previous chapters, neurophysiological and neuropsychological test results were investigated in young schizophrenic patients to gain insight into pathophysiological mechanisms underlying abnormal brain function in recent-onset schizophrenia. In this last chapter, a tentative effort is made to integrate the findings from the studies described in the previous chapters into one model of the neurobiology of schizophrenia.

Because schizophrenia is such a prevalent and serious disorder, it has been the subject of many theories and models. Kraepelin, the founder of modern psychiatry, united several psychiatric syndromes (hebephrenia, catatonia and paranoia) in one concept: dementia praecox. The term 'schizophrenia' was introduced by Bleuler in 1911.

Other competing models for conceptualizing schizophrenia, which, although seriously debated in the past, are presently dismissed as demonstrably invalid or so reductionistic as to not account for major observations associated with the illness. Non-disease models, such as the societal reaction theory ("a sane reaction to an insane world") or Thomas Szasz's theory that schizophrenia is a myth enabling society to manage deviant behavior, cannot adequately account for the distribution of schizophrenia among biological relatives, the myriad of associated brain abnormalities and the normalizing effects of drug treatment. Furthermore, it cannot explain the similarity, lifetime prevalence and clinical manifestations of schizophrenia across widely divergent cultures. The many biological, psychological, and social factors relevant to the understanding and treatment of schizophrenia require a broad model and eschew reduction to any single level of the functioning organism (Kaplan and Sadock, 2000).

Despite controversies, consensus has emerged in the previous decades that a genetic factor plays a role in the etiology of schizophrenia. Family, twin, and adoptive studies have documented a robust contribution of genetic factors to the etiology of schizophrenia, with genetic factors established as relevant to some, perhaps all, cases. Schizophrenia and schizophrenia-related disorders, such as schizotypal, schizoid and paranoid personality disorders; schizotypic disorder; and other nonaffective psychotic disorders, occur at an increased rate among the biological relatives of patients with schizophrenia. This increased rate is most dramatically illustrated in the case of monozygotic twins, who have an identical genetic endowment and a concordance rate for schizophrenia between 40 to 50 percent. This rate is four to five times greater than the concordance rate in dizygotic twins or the rate of occurrence found in other
first-degree relatives. The role of genetic factors is further reflected in the drop off in occurrence of schizophrenia among second- and third-degree relatives, in whom one would hypothesize a decreased genetic loading. The finding of a higher rate of schizophrenia among the biological relatives of an adopted-away person who develops schizophrenia, as compared to the adoptive, non-biological relatives who rear the patient, has added further support to the overwhelming pedigree and twin study evidence suggesting a significant genetic contribution to the etiology of schizophrenia.

The genetic factor in the present model is hypothesized to be an unstable, labile nervous system, i.e., a nervous system that has difficulty maintaining homeostasis. Homeostasis consists of an optimal level of arousal. A reduced ability to maintain homeostasis may be present from birth, in a less extreme form than after onset of schizophrenia and it may become apparent in e.g., shyness and fearfulness. After onset of schizophrenia, arousal may be too high in a psychotic episode. However, in subsequent negative episodes, arousal may be too low as indicated by a reduced P300 amplitude in the second P300 session (chapter 5). Dysfunction of the nucleus reticularis of the thalamus with concomitant deficits in sensory gating, may play a role in excitability dysfunctions (chapter 4).

Too much (dopaminergic) stimulation associated with hyper-arousal and too little inhibition for extended periods can lead to neuronal death. Several studies have shown a reduction in brain volume in patients with schizophrenia compared to control subjects. Research into new antipsychotic medication, indicates that it should be possible to alleviate psychotic conditions by stabilizing rather than paralyzing neurocircuits, thus avoiding the risk of motor and mental side effects of the currently used drugs. Among these new classes, dopaminergic stabilizers seem to offer most promise at present (Carlsson et al., 1999).

Pathophysiological mechanisms underlying brain dysfunction in schizophrenia

In this thesis, neurophysiological and neuropsychological assessments have been used to investigate brain dysfunction in recent-onset schizophrenic patients. The chapters dealing with antisaccades and visual scanning (chapter 2 and 3) both clearly indicated disturbed functions of the prefrontal lobe, more specifically, Brodmann area 46, i.e. working memory.

Prefrontal lobe dysfunction may lead to reduced ability to inhibit reflexive motor
processes, e.g., saccades and possibly also to reduced ability to inhibit or diminish reflexive thought processes. A psychotic thought (e.g. I am the victim of a conspiracy) could be considered as a reflexive thought without diminution in the form of self-reflection. Healthy people may have the same reflexive thought for a moment but diminution of the thought by means of self-reflection usually induces a more realistic view of the situation. A psychosis has been compared with a dream or nightmare in a waking state (Hartman, 1975; Itil, 1970; Hernandez-Peon 1966). A dream or nightmare is also a reflexive mental state without reflection. The effect of absence of reflection can be felt when one is awakening from a nightmare. The terror dissolves with the increment in reflection and rational thought. Perhaps the biological mechanisms of the moment in which a dream disappears and the self-reflecting part of the mind takes over in a healthy person, should be investigated in more detail with for example EEG, fMRI or other brain imaging techniques. If more insight is gained into these mechanisms, that are clearly disturbed in a patient with schizophrenia, they could maybe be influenced.

Another example showing that reflection is needed for mental health is the following situation. Walking into a room with people laughing can invoke the thought in the person entering that those people were laughing about him- or herself. Most people are able to reflect on the thought, to convince themselves that it is probably not true. A person in a psychotic state could not reflect on the thought, could not convince himself, and could certainly not be convinced by others.

A crucial aspect in the schizophrenia disease process may be the inability to self-reflect. If a patient in a psychotic episode could reflect on his own delusional thoughts and conclude that what he thinks cannot be true, the psychosis would not exist. The onset of schizophrenia is usually late adolescence or early adulthood. In this period, the executive functions of the prefrontal lobe become more and more important in daily life to meet stressful new demands on cognition and interpersonal skills. It is also only in this period that the frontal lobes become fully developed.

Schizophrenia seems to be associated with an inability to actively control initial responses. The often spiritual and religious content of delusions and hallucinations may also relate to an internal propensity, maybe genetically determined, of the human psyche for spirituality. A common delusion in western patients with schizophrenia is to be a special messenger of God or Jesus himself (Kay et al, 1987; Kirov et al, 1998; Podvoll, 1999). Eastern schizophrenic patients may have the same delusion with a more eastern content. The eastern schizophrenic patient may for
example think to be Buddha (Visser and Nieman, 2000).

Self-reflection may be partly related to a continuum of arousal-relaxation. At the outer extreme of arousal e.g., occurring in a life-threatening situation, self-reflection is usually reduced in healthy subjects.

Patients with brain damage of the frontal lobe have several clinical features in common with schizophrenic patients, such as deficient abstract thought, self-reflection and strategic ability. However, patients with prefrontal lobe damage usually do not suffer from positive symptoms and memory dysfunctions that are so prominent in schizophrenic patients. Thus, disturbed functioning of another neuroanatomical area of the brain may be implied in schizophrenic pathology. In chapter 5, relationships between P300 characteristics, neuropsychology and symptomatology suggest that temporal lobe function also plays a role in the genesis of schizophrenia. Reduced parietal P300 amplitude may signify dysfunctions in 'mediate-term' memory. These memories are needed for the correct interpretation and understanding of the current situation. When the continuous stream of memory updating is deficient, experiences may become fragmented and distorted. The combination of the prefrontal dysfunction in self-reflection and the temporal dysfunction in mediate-term memory may lead to a reduced ability to actively participate in a complex society.

Other studies have also reported prefrontal and temporal dysfunctions in schizophrenia. The demonstration of decreased volumes of prefrontal gray or white matter, prefrontal cortical interneuron abnormalities, disturbed prefrontal metabolism and blood flow, decreased volumes of hippocampal and entorhinal cortex, and disarray or abnormal migration of hippocampal and entorhinal neurons provide strong support for the involvement of these brain regions in the pathophysiology of schizophrenia. Furthermore, the observation of the relationship between impaired Wisconsin Card Sort Test performance, diminished prefrontal cortex blood flow and diminished hippocampal volume provides support for the validity of prefrontal cortex and limbic system neuroanatomical models (Kaplan and Sadock, 2000).

Symptomatology
Positive symptoms were not related to any of the test results in the present thesis. This conclusion is in accordance with previous research findings in the same patient group (Van der Does et al., 1993). Positive symptoms were also not predictive of performance on neuropsychological and neurophysiological tests. In contrast, several
relationships were noted of negative and disorganization symptoms with neuro-
physiological test results.

Negative symptoms in young patients with schizophrenia were related to a time
dependent decrease in P300 amplitude (chapter 5). The reduction of P300 amplitude
in the second P300 session compared to the first P300 session in patients with negative
symptoms may be caused by a time dependent increase in the threshold for neuronal
firing. This increase in threshold may diminish the number of firing neurons, inducing
a reduction of P300 amplitude. The reduced number of firing neurons may underlie
the clinical symptom of inhibited responsiveness to external stimuli. Negative
symptoms are still difficult to treat with medication or other therapeutic interventions.
Future research on drugs to alleviate negative symptoms could perhaps also take into
consideration an increased threshold for neuronal firing as a pathological mechanism
in negative symptoms. In the development of new treatments for schizophrenia, it
may be of prominent importance to relate clinical symptoms to their biological
substrates, even on the level of the individual cell.

We have not found a relationship between negative symptoms and prefrontal
dysfunction, as previously reported in studies using functional MRI. Regarding the
findings in our P300 study (chapter 5), the relationship between the prefrontal lobe
and negative symptoms may also be associated with a more rapid decrease in
performance over time in patients with negative symptoms. Compared to other
cognitive functions, the executive functions of the prefrontal lobe place the largest
demand on the limited energy resources of a schizophrenic patient with negative
symptoms. Thus, the executive functions may need more energy resources than
available in a patient with negative symptoms.

In chapter 2, a relationship was demonstrated between increased antisaccade
latency and increased disorganization symptomatology. In chapter 3, dealing with
visual scan patterns, a relationship was found between increased fixation duration
and more severe disorganization symptomatology. Prolonged fixation duration was
also related to prolonged time to complete copying the Complex Figure of Rey. In
the process of copying, the eyes are repeatedly focused on the complex figure to
obtain information. If patients have a prolonged fixation duration, the time to complete
the copy increases. The prolonged fixation duration implies that information about
the complex figure is not processed at a normal pace. Positive symptoms fade in most
young patients over a period of weeks and negative symptoms are usually not as
pervasive as in older, more chronic patients. Disorganization symptoms in young schizophrenic patients with concomitant difficulties in information uptake and processing may lead to difficulty in returning to study, job and daily life in general.

Disorganization symptomatology is probably not related to dorsolateral prefrontal cortex dysfunction because a relationship of disorganization symptomatology with antisaccade error rate was absent. Increased severity of disorganization symptoms at intake was related to reduction of posterior P300 amplitude recorded about six weeks after assessment of symptoms (chapter 5). Disorganization symptoms may affect posterior P300 amplitude in a more stable manner. Reduced P300 amplitude has often been found to relate to disorganized thought (Higashima et al., 1998; Juckel et al., 1996; Iwanami et al., 2000). Disorganized thought has been described as a trait marker because of its persistent and stable nature (Marengo and Harrow, 1997) and its presence in subjects with a high risk for schizophrenia (Parnas and Schulsinger, 1986). Temporal lobe structures are probably involved in posterior P300 amplitude generation (chapter 5). Therefore, disorganization symptomatology may be related to disordered temporal lobe function. Unfortunately, disorganization symptoms are difficult to treat, like negative symptoms. In the development of new drug treatments of disorganization symptoms, progress in the neurosciences concerning normal and disturbed functioning of the temporal lobe may be important.

Antipsychotic medication
Risperidone and olanzapine displayed differential effects on reflexive saccades and parietal P300 amplitude. Risperidone was associated with prolonged latencies of reflexive saccades and reduced P300 parietal amplitudes compared to olanzapine. One of the differences in the receptor binding profile between olanzapine and risperidone concerns the alpha₂ adrenergic receptor. Risperidone is an alpha₂ receptor antagonist whereas olanzapine is not. The alpha₂ receptor agonist clonidine improves performance on the spatially delayed response task in monkeys (Arnsen and Goldman-Rakic, 1985). In addition, performance on tests of learning and memory was significantly improved in schizophrenic patients with the alpha₂ receptor agonist clonidine. In our study about the P300 (chapter 5) risperidone was associated with reduced parietal P300 amplitude that was associated with poorer performance on neuropsychological tests of memory. From these findings it may be suggested that the alpha₂ adrenergic antagonism of risperidone may influence memory negatively in schizophrenic patients. Furthermore,
the alpha, receptor agonist guanfacine has been reported to improve reaction time in healthy subjects (Kugler, 1980). In chapter 2, risperidone was associated with prolonged reaction times of reflexive saccades compared to olanzapine.

Unanswered questions
The close association of mind to brain might lead us to suspect uncritically that mind and brain are the same, which would be as invalid as stating that the islands of Langerhans of the pancreas are the same as insulin regulation of glucose metabolism. Minding is a function of the entire organism interacting with its environment, just as glucose metabolism is a function of the organism metabolizing environmentally derived nutrients (Pribram, 2000).

Thus, although the special relation between brain and conscious experience is widely acknowledged, the subtleties inherent in the nature of the relation remain debatable. In this respect apparently no progress has been made in the past two millennia.

The theories in the sixties and seventies may have been proven invalid in accusing the patients' family or environment for the psychotic illness and in rejecting antipsychotic medication, they may not have been invalid in taking a phenomenological stand in trying to assess and understand schizophrenia. A similar approach is returning recently (Møller and Husby, 2000) as it slowly becomes apparent that investigating the various major and minor biological dysfunctions in schizophrenia has not resulted in breakthroughs in schizophrenia research. Schizophrenia is mainly characterized by distorted experiences and thoughts of the patient. In a study of Møller and Husby (2000), subjective experiences in a prodromal phase of schizophrenia were explored to increase understanding of the schizophrenic disease process. The authors took a phenomenological stand and deduced core dimensions of experience and behavior from extensive interviews held with the patients. For example, the authors argued for 'extreme preoccupation by and withdrawal to overvalued ideas (e.g. preoccupation with religious mysticism/philosophy)' as a core dimension. The naturalistic, phenomenological approach of Møller and Husby is supported by our findings that the subjective experiences of patients are closely correlated with an extensively investigated biological marker like the P300. In future studies, different aspects of the subjective experience of schizophrenic patients may be investigated on their relationship with biological markers to gain more insight into the schizophrenic disease process and its biological substrate.
The unresolved issue of how the psyche is generated by the body (Damasio, 1994; Rose, 1998) may also play a role in the absence of breakthroughs. The exact biological substrate of a thought is at the current state of science unknown, illustrated by the fact that it is impossible to visualize the content of a thought with modern brain imaging techniques. Brain activity can be visualized on a computer screen with MRI scans but assessing with these scans the content of the brain activity (the thought) is as yet impossible.

The subjective experience of the patient with schizophrenia remains qualitatively different from neurophysiological and neuropsychological test results. The mind-body problem has not yet been solved. Treatment of and research into schizophrenia should not only focus on disturbed brain function but also on subjectively experienced psychological and social-relational problems of the patient with schizophrenia. Treatment that only consists of prescription of medication is often experienced as reductionistic by the patient and appears less effective than a combination of psychosocial treatment and medication (Carpenter, 1993; Linszen et al, 1996).

Future research

Data on monozygotic twins clearly demonstrate the fact that individuals who are genetically vulnerable to schizophrenia do not inevitably become schizophrenic; environmental factors must be involved in determining a schizophrenia outcome. If a vulnerability and liability model of schizophrenia is correct in its postulation of an environmental influence, then other biological or psychosocial environmental factors may prevent or cause schizophrenia in the genetically vulnerable individual. Possible environmental factors include risk factors, such as stress (Kaplan and Sadock, 2000).

Primary prevention

The heterogeneous course and outcome of schizophrenia is skewed heavily in the direction of chronicity and life-long disability (McGlashan, 1999). Early in the course of the illness changes take place that make a full recovery of schizophrenia unlikely. Early recognition of the disorder has proven to contribute significantly to a better prognosis (McGlashan 1998; Linszen et al, 1995). Intervention even before the first psychotic episode may be the best way to prevent the brain damaging changes that take place during the course of schizophrenia.

Identifying patients in a prodromal phase of the illness is still problematic.
Neurophysiological and neuropsychological dysfunctions could be useful in differentiating the patients in the true prodromal phase of schizophrenia from other subjects. Data on the usefulness of neurophysiological and neuropsychological test results in primary prevention of schizophrenia are scarce.

If children with a high risk for schizophrenia could be reliably identified before the first psychosis, it may be possible to prevent the onset of schizophrenia. More research is required into methods for reliably identifying subjects at true risk for schizophrenia and into methods for preventing the onset of schizophrenia.

In the Adolescent Clinic of the Academic Medical Center a program designed for young schizophrenic patients has proven to be effective in reducing psychotic relapses (Linszen et al 1996). This program entails an assessment of the risk and protective factors of the patient. The doctor and patient together make a list of stress reducing and stress increasing events and activities for this individual patient. The patient uses this list in his daily life to reduce stress to manageable proportions. Additional psycho-education helps in increasing awareness in the patients of the risks of, e.g., drug use. The same program may be effective in primary prevention. Low doses of antipsychotic medication could be given to some patients with overt psychotic symptoms. Future research may investigate the usefulness of this program in primary prevention.

Genetic research
Performance on neurophysiological and neuropsychological tests, like the antisaccade task, event-related potentials and neuropsychological tests sensitive to attentional dysfunctions is also diminished in approximately half of the first-degree relatives of patients with schizophrenia. These test results are hypothesized to reflect the genetic vulnerability in otherwise well first-degree relatives of the patient. The P50 ERP defect has been shown in a genetic linkage study to be localized on chromosome 15. Other neurophysiological and neuropsychological tests may also be useful in genetic linkage studies to find the schizophrenia susceptibility genes.

Course of schizophrenia
The course of schizophrenia varies widely, from a single psychotic episode with no residual symptoms via multiple psychotic episodes to chronic psychosis with strongly reduced behavioral functioning. It is not possible to give a prognosis in the early phase of the disease and adjust treatment plans accordingly. The neurophysiological
and neuropsychological assessments described in this thesis could be investigated as predictor of the course and outcome of schizophrenia.

In the first five years after onset of schizophrenia, often referred to as the critical phase, the course of the disease will become apparent. To gain more insight into underlying biological mechanisms that may determine the course of schizophrenia, patients could be tested again five years after the first time of testing. The pattern of neurophysiological and neuropsychological test results may provide a better understanding of pathophysiological mechanisms associated with a more benign or deteriorating course. For example, the previous project has shown that reduced antisaccade task performance is related to prefrontal lobe dysfunction (Nieman et al, 2000) whereas reduced amplitude of the P300 event-related potential seems indicative of temporal lobe dysfunction (Nieman et al, in press). If most patients with a deteriorating course have increased reduction of P300 amplitudes and stable antisaccade task performance, it may be hypothesized that temporal lobe dysfunction is associated with a deteriorating course. It has not yet been investigated how the pattern of neurophysiological and neuropsychological test results changes over a period of five years in a group of young recent-onset schizophrenic patients.

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