ABSTRACT

Schizophrenia is a severe psychiatric illness. It affects young people and often results in lifelong complications such as a distorted perception of reality, decreased cognitive ability and impairment in the realms of motivation and emotions. There is no effective treatment available for two of the symptom domains: cognitive symptoms and the so-called negative symptoms. In recent years, attention has been drawn to the fact that these are the symptom domains resulting in the greatest functional impairment and which best predict a negative prognosis. The need for increased knowledge of the underlying neurobiological correlate is therefore great. Another aspect of the disease - diagnosis in the new onset phase - is an area also requiring more attention, as it is of the utmost importance that a reliable diagnosis be made quickly in order that the correct treatment may be initiated. This thesis describes four studies carried out by myself and my colleagues. Each study addresses different aspects of these schizophrenia-related problems. Diagnostic stability (DS) in the new onset phase of schizophrenia and other psychotic disorders was investigated in the first study. The diagnostic development was analyzed in material documenting 146 first episode psychosis patients that were followed prospectively and longitudinally over 3 years. A large variation in DS was found between the various diagnoses and diagnostic groups. Generally, schizophrenia and the schizophrenia spectrum had high DS, while the DS of diagnoses such as delusional disorder and schizoaffective disorder was low. On the basis of this it is suggested to be restrictive in the use of specific diagnoses in the early phase of a psychotic disorder. The second study examined whether the network of brain regions which processes cognitive control activates different circuits depending on whether the distraction to be processed in parallel with solving a task is of a cognitive or affective nature. A group of 11 healthy subjects were asked to perform counting Stroop (cStroop) and affective counting Stroop (aStroop) during one session while being scanned by a magnetic resonance imaging (MRI) camera. The blood oxygen level dependent (BOLD) functional MRI (fMRI) data shows that this division is present not only in the anterior cingulum cortex (ACC) as expected from previous studies, but also in the dorsolateral prefrontal cortex (DLPFC). This implies separate circuits within the cognitive control network for affective and cognitive distractions. The third study was devoted to the neurochemical regulation of the cognitive control network. Pharmaco fMRI technique was used to investigate whether brain regions, as
activated by aStroop and cStroop respectively, react differently to the selective serotonin reuptake inhibitor (SSRI) agent escitalopram when it is used as a pharmacological probe. A group of 11 healthy subjects performed aStroop and cStroop while being scanned by an MRI camera. Escitalopram was administered after the first session, and the subjects repeated the same examination after a period of four hours. It was found that activation in the rostral ACC by aStroop was significantly decreased following intake of escitalopram. The implication is that the ability to pursue goal-oriented behavior while being disturbed by affective stimuli - an ability which is often impaired in states such as schizophrenia - may be improved on administration of an SSRI.

The amygdala’s involvement in the negative symptoms of schizophrenia was examined in the fourth study. The amygdala is a region in the medial temporal lobe of the brain which is critical to faculties such as assigning value to affective stimuli. It was found that the volume of the amygdala as measured by MRI and the activity of the amygdala during an affect inducing paradigm called the Face Matching Task paradigm as measured by BOLD fMRI had a negative correlation to the level of negative symptoms in a group of 28 schizophrenia patients. No significant difference was however found in the volume or activity of the amygdala between this group of patients and a group of 28 matched healthy control subjects. We believe this indicates that the amygdala is involved in the neurobiology of negative symptoms.
LIST OF PUBLICATIONS


III. Rahm C, Liberg B, Aspelin P, Kristoffersen-Wiberg M, Msghina M.

Differential effects of single-dose escitalopram on cognitive and affective interference during Stroop task. *Submitted.*


Negative symptoms in schizophrenia show association with amygdalae volumes and neural activation during affective processing. *Submitted.*
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACC</td>
<td>Anterior cingulate cortex</td>
</tr>
<tr>
<td>APA</td>
<td>American Psychiatric Association</td>
</tr>
<tr>
<td>AUDIT</td>
<td>Alcohol Use Disorders Identification Test</td>
</tr>
<tr>
<td>BET</td>
<td>Brain Extraction Tool</td>
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<td>BOLD</td>
<td>Blood oxygen level dependent (data)</td>
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<td>DLPFC</td>
<td>Dorsolateral prefrontal cortex</td>
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<td>DS</td>
<td>Diagnostic stability</td>
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<tr>
<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual, 4th edition</td>
</tr>
<tr>
<td>DSM-5</td>
<td>Diagnostic and Statistical Manual, 5th edition</td>
</tr>
<tr>
<td>DUDIT</td>
<td>Drug Use Disorders Identification Test</td>
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<td>fMRI</td>
<td>Functional Magnetic Resonance Imaging</td>
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<tr>
<td>FEAT</td>
<td>FSL Expert Analysis Tool</td>
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<tr>
<td>FILM</td>
<td>FMRIB's Improved Linear Model</td>
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<tr>
<td>FLAME</td>
<td>FMRIB's Local Analysis of Mixed Effects</td>
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<tr>
<td>FLIRT</td>
<td>FMRIB's Linear Image Registration Tool</td>
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<tr>
<td>FMRIB</td>
<td>Oxford Centre for Functional Magnetic Resonance Imaging of the Brain</td>
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<tr>
<td>FSL</td>
<td>FMRIB Software Library</td>
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<tr>
<td>ICD-10</td>
<td>International Classification of Disease, 10th edition</td>
</tr>
<tr>
<td>MATRICS</td>
<td>Measurement and Treatment Research to Improve Cognition in Schizophrenia</td>
</tr>
<tr>
<td>MNI152</td>
<td>A standard brain template produced by Montreal Neurological Institute, based on the average of 152 normal MRI scans</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>NMDA</td>
<td>N-methyl-d-aspartate</td>
</tr>
<tr>
<td>PANSS</td>
<td>Positive and Negative Syndrome Scale</td>
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<tr>
<td>PFC</td>
<td>Prefrontal cortex</td>
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<tr>
<td>Pharmaco-fMRI</td>
<td>Pharmacological functional Magnetic Resonance Imaging</td>
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<tr>
<td>Prime-MD</td>
<td>Primary Care Evaluation of Mental Disorders</td>
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<tr>
<td>SCID-1</td>
<td>Structured Clinical Interview for DSM-IV</td>
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<tr>
<td>SIENA</td>
<td>Structural image evaluation, using normalization, of atrophy</td>
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<tr>
<td>SIENAX</td>
<td>An adaptation of SIENA for cross-sectional measurement</td>
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<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>SSRI</td>
<td>Selective serotonin reuptake inhibitor</td>
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<tr>
<td>T</td>
<td>Tesla</td>
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<tr>
<td>TE</td>
<td>Echo time</td>
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<tr>
<td>TR</td>
<td>Repetition time</td>
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<tr>
<td>TOP</td>
<td>Thematically Organized Psychosis (study)</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>5-HT</td>
<td>5-hydroxytryptamine, i.e. serotonin</td>
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1 INTRODUCTION

The ability to perceive and understand what is happening within and around oneself, and to adapt flexibly to the ever-changing nature of this environment places great demands on the different parts of the brain and the integration of their functions. Psychotic illnesses, especially schizophrenia, interact with central processes involved in these tasks and optimal performance in a great many areas is thus limited. The capacity to deal with everyday life decreases; thinking becomes disordered; the emotional life and motivation do not function as previously and the experiential world is changed in a way that is often frightening. Schizophrenia is one of the most serious illnesses from which one can suffer.

There are crucial pieces of the puzzle missing in our understanding of the disease and we need more alternatives in our treatment arsenal, particularly in regard to the cognitive and negative symptoms. These account for most of the functional impairment and are predictors for poor prognosis. Furthermore, it is not certain which is the most suitable diagnostic method for a psychotic patient presenting for the first time.

In this thesis I wanted to investigate these aspects of schizophrenia: the diagnostic stability in the new onset phase, and the neural underpinnings of some core cognitive and negative symptoms.

The reader will be guided through my work over the course of the thesis. Following a presentation of the aims of the research and our hypotheses I will provide a background so the problems are placed in a context. I will then discuss which methods we have used and the study populations to which I have had access. This is followed by a chapter about our results. In the concluding chapter I will discuss the possible implications of the results.
1.1 AIMS

I aimed to study the following:

1) Diagnostic stability in the new onset phase of schizophrenia and other psychotic disorders. I wanted to perform a descriptive explorative study of this area without being restrained by a specific hypothesis.

2) Neural correlates of cognitive control. The hypothesis was that different circuits in the networks of the brain regions which manage cognitive control are involved depending on whether the distraction to be processed is cognitive or affective.

3) Neurochemical regulation of cognitive control. Our hypothesis was that serotonergic systems regulate cognitive control for affective distractions to a greater extent than for cognitive distractions.

4) Neural correlates to negative symptoms. My hypothesis was that the volume and function of the amygdala is abnormal in the case of schizophrenia, and that this correlates to the intensity of negative symptoms.

1.2 LITERATURE REVIEW

1.2.1 Schizophrenia

1.2.1.1 Disease Characteristics

Schizophrenia symptoms most often make their debut in young persons of 20-30 years, just as they are starting off in life. It is a cruel disease which curtails the possibilities of a free independent lifestyle and causes much suffering to the afflicted and those close to them. The functional impairment persists for a long time period and involves several vital areas of mental function. Although some patients recover spontaneously after 10-15 years, the majority experience lifelong symptoms. The disease has a reasonably even spreading over different cultures and levels of society, has around the same prevalence amongst women and men, and does not seem to be increasing or decreasing
in its prevalence, of just under 1% (1). Schizophrenia leads to social stigmatization now as it has done in the past, not only because of the portrayal of the disease in mass media and popular culture but also because of the fact that the individual patient’s behavior often causes him or her to stand out from the rest of society (2).

The list of disease criteria in current diagnostic systems, Diagnostic and Statistical Manual, 5th edition (DSM-5) and International Classification of Disease, 10th edition (ICD-10) may be useful clinically. In cases involving complex differential diagnosis it is worthwhile to revisit the list for guidance. However, the list names nothing of the underlying disease mechanisms which resulted in the condition, whether there are genetic or nervous system effects, which anomalies should be expected to be seen in brain imaging or on psychological tests, or the social or existential effects on the individual (figure 1).

These dimensions must of course be taken into consideration when meeting individual patients and in the context of research. In the work that follows I am particularly interested in neurobiological correlates.

I have based my work on the division of the manifestations of schizophrenia into three domains: positive, cognitive and negative symptoms (3). This is a division which was established in the 1980s, and which has stood its ground and survived various other initiatives to subdivide the disease.

1.2.1.1 Positive Symptoms

Positive symptoms traditionally refer to hallucinations and delusions. These are perhaps the most obvious characteristics of schizophrenia. The most common type of hallucination is the auditory sort. It is most commonly voices that are heard, sometimes several voices at once. The voices make condescending comments about what the person is doing, or exhort the person to do something. Hallucinations can also involve taste, smell or other sensory modalities.
**DSM-5 criteria for schizophrenia**

**A. Two or more of the following:**

Delusions
Hallucinations
Disorganized speech
Grossly disorganized or catatonic behavior
Negative symptoms

**B. Level of functioning in work, interpersonal relations, or self-care is markedly below the level achieved prior to the onset.**

**C. Continuous signs of the disturbance persist for at least 6 months.**

**D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out.**

**E. The disturbance is not attributable to the physiological effects of a substance or another medical condition.**

**F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are present.**

**Figure 1.** Schizophrenia is described as a combination of various symptoms in the current diagnostic systems for psychiatric diseases, Diagnostic and Statistical Manual, 5th edition (DSM-5). Both criterium A, B, C, D, E, and F need to be fulfilled.
Delusions may concern many things but often follow the theme of being pursued or monitored, or that someone is wishing the patient harm. These symptoms may be extremely agonizing, especially in the initial stage of the disease and during acute relapses, but over the years patients usually learn to distinguish between reality and non-reality, even if the psychosis does not disappear altogether.

The greatest effect of medication and psychotherapy is on positive symptoms (4-7).

### 1.2.1.1.2 Cognitive Symptoms

Currently there is growing interest in the cognitive symptom domain, as these symptoms are deemed to be the major underlying cause of the loss of function associated with the illness (8-10). To some extent this constitutes a revival of the approach to schizophrenia which was prevalent around the turn of the last century when the first major studies of the disease were carried out (11, 12). The term dementia praecox was the initial term for the condition we now call schizophrenia, and this term was chosen because the central phenomenon in the disease was considered to be an adolescent onset cognitive deterioration. The cognitive symptoms have also shown themselves to be a strong predictor for poor long-term prognosis, and an effective pharmacological treatment is as yet unavailable (13).

The cognitive symptoms can be summarized as comprising a type of dysexecutive syndrome. Behavior and speech become fragmented and actions become irrational and disorganized. Consequences can include for example difficulty in completing studies, maintaining employment, managing private finances or, for that matter, compensating for other handicaps associated with the disease.

Cognitive impairment can be observed in patients’ decreased level of performance in neuropsychological tests. Compared with the average population, schizophrenia patients score around one standard deviation less in a great number of tests (14). However, a growing body of work implicates that the core cognition deficits are
reduced working memory, impaired episodic memory and impaired cognitive control (13, 15). The latter, a sort of reduced self-regulation capacity leads to severe difficulties in the optimal regulation of ones behaviour (16). The schizophrenic patient is more easily distracted and has difficulty ignoring impulses, interruptions and peripheral thoughts. Although not important in the context, these distractions catch and maintain the attention and it becomes difficult for the individual to accomplish what they had set out to do (17).

Since this function, cognitive control, is the focus of two of my studies, studies 2 and 3, I will make a digression on this subject.

An operational definition of cognitive control is the ability to maintain and adapt a targeted behavior in an optimal manner through the use of continuously updated problem solving while being exposed to distractions and unexpected input (18, 19). Two brain areas in particular have been implicated as mediators of cognitive control: the anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex (DLPFC) (20). The ACC appears to be involved in detecting errors in the form of distracting or interfering stimuli (21, 22) while the DLPFC appears to be involved in resolving cognitive conflicts through the use of focused attention and problem solving (23). One test which is considered to pinpoint cognitive control is the Stroop test (24), which is further described below.

There is much to suggest that serotonin and dopamine are involved in the neurochemical regulation of the cognitive control neural networks (25, 26). Studies have been conducted with research subjects receiving tryptophan depleted diet, thereby decreasing the availability of serotonin in the synaptic clefts; this resulted in increased activity in the ACC when the aStroop test was performed (27). Several studies have shown that the use of prodopaminergic agents was associated with a change in the activity of the DLPFC parallell to improved cognitive control (28).
1.2.1.3 Negative Symptoms

In addition to positive and cognitive symptoms, negative symptoms are involved in schizophrenia. The term itself derives from the context of neurology and epilepsy where negative symptoms means deficiency, i.e. that the patient lacks some psychological capacities that was usually present.

The negative symptoms of schizophrenia are subdivided into affective and conative symptoms (29). Affective negative symptoms consist of anhedonia which involves an inability to feel happiness when something positive occurs, social withdrawal where the patient keeps to themselves, as well as blunted affects involving a loss of nuanced affect expression. Neuropsychologically, blunted affect is characterized by aberrant affective identification and affect expression (30). The dominating conative symptom is amotivation - the inability to carry out tasks that one realizes one should. Loss of motivation is associated with an impaired level of function, decreased response to treatment and a chronic prognosis (31).

There are few disabilities that are so negatively interfering with the development of relationships and maintaining of social networks as abnormalities in emotional interaction. The consequences of negative symptom are often loneliness and social rejection (32).

1.2.1.2 Causes of Schizophrenia

Although the aetiology of schizophrenia is still a riddle, an integrative working model has emerged based on data from multidisciplinary studies. It is called the neurodevelopmental model of schizophrenia (33-37). It was formulated in the mid-1900s when a great deal of brain development knowledge was compiled; it was found that the brain underwent many phases during childhood and that not everything was related to learning. It was seen that there is scope for interference to occur very early in
life that only results in symptoms decades later. Since then the model has been
developed and it now includes the latest research results.

In short, the neurodevelopmental model of schizophrenia states that the disease
processes are active for a significant period of time before the initial symptoms become
clear, most probably from the time of the establishment of the central nervous system.
It is assumed that this is mostly genetically driven; for example, several vulnerability
genes code for proteins that are involved in synaptogenesis and signal transfer between
nerve cells (38). The model suggests that in addition to inherited vulnerability factors it
is necessary that environmental stress factors be present for the disease to develop. If
these “hits” occur during a sensitive phase of the brain’s continuing development they
may stimulate disease development (39, 40). Early events such as prenatal viral disease
or complications at birth may be able to cause neuronal dysplasia. Factors associated
with late adolescence such as drug abuse or excessive pruning may lead to the initial
episode of the disease. A third wave of “hits” may occur when the disease is already
manifest, such as the excitotoxic consequences of glutamatergic dysregulation which
may give rise to continued deterioration in a subgroup of patients.

According to this model, when the first symptoms appear in late adolescence they are
preceded by a longer time period with more latent disease development.

The advantage of the model is that it provides a greater framework for our
understanding of the disease and its progression. The theory is of such a general nature
that both theories on the importance of genetic factors are incorporated, as well as
neurochemical abnormalities and observations on the disconnectivity in the brain’s
fiber bundles. The disadvantage is that the theory is so open to speculation that it is
difficult to imagine an observation that falsifies the theory; for this reason the theory is
of limited use.
The neurochemical abnormality present schizophrenia that has traditionally been discussed the most is the so-called dopamine hypothesis, which hypothesizes an imbalance in the dopaminergic system (41). The hypothesis is that, at the same time as a hyperdopaminergic state is present in the subcortical mesolimbic pathway - possibly mediating the positive symptoms - a hypodopaminergic state is present in the prefrontal cortex via the mesocortical dopamine pathway - possibly mediating the negative and cognitive symptoms. However, due to methodological issues it has been difficult to test all parts of the hypothesis.

In recent years another theory regarding the neurochemistry of the disease has also gained ground. This theory states that the central abnormality of the chemical regulation of the brain is underfunctioning of the NMDA glutamate receptor (42, 43), a receptor present in large amounts in almost the entire brain. There are also models that join together the glutamate and dopamine models, claiming that imbalance in the dopaminergic system is linked to functional impairment in the glutamate transmission (44).

1.2.1.3 Diagnosis

The diagnosis of a patient with suspected schizophrenia can be a difficult process. Since it determines much of the treatment and reasoning about the prognosis, it is important that a correct diagnosis is made. When informing of the diagnosis schizophrenia, the diagnosis should be well grounded because many processes are initiated in the patient, the patient’s family and in the health care system.

The diagnostic process for schizophrenia is basically the same as for any other disease. It is based on a thorough patient history, a complete medical examination, observations made over time and where necessary supplemented with other investigations such as blood tests, psychological tests, electrophysiology or brain imaging (45). The diagnosis of schizophrenia is wholly clinical as there are no biomarkers for clinical use.
In the early stages of the disease it can be especially difficult to find a sufficient basis for a complete diagnosis. This is partly due to practical difficulties in carrying out the entire investigation (46), and partly due to the complicating factor of fluctuations in the manifestation of the disease over time (47, 48). It is therefore not uncommon that the initial diagnosis made for a patient presenting with their first episode of psychosis is often revised at a later point.

In light of this there is an increasing interest in the diagnostic stability (DS) of psychotic syndromes, meaning the extent to which the initial diagnosis still holds true at a later stage. When it is possible to define a disease in a way that results in high DS, this suggests that the definition is also valid and has actually managed to pinpoint a disease process (49). If the stability of diagnosis is certain, this also facilitates in the research context (50) and is of clinical interest for treatment and prognostic considerations (51).

The first study of this thesis examines the DS of psychotic disorders.

1.2.1.4 Treatment

How is this difficult disease to be treated? The WHO lists schizophrenia as one of the ten most severe diseases in the world (52).

The combination of treatment with medication, social intervention and psychological therapy are recurring elements in many treatment guidelines (53). Without wishing to diminish the other two components of treatment I will make a digression here regarding medication, as this links directly to the third study in my thesis.

A large number of preparations have been tested to see if they can provide relief for schizophrenia patients. Those which have proven effective and come to form the standard treatment are the so-called neuroleptics (neuro - sense, leptic - capture), also known as antipsychotics. All antipsychotics have the same central mechanism of action, which is to suppress transmission through the brain’s dopamine D2 receptors.
In addition to this, antipsychotics also interact with other neurochemical systems in the brain. Many of the second generation antipsychotics also stimulate the serotonin system and modulate its 5HT2A receptor. It is difficult to determine what consequences this may have; it is possible that it reinforces the antipsychotic effect, partly suppresses the negative consequences of the dopamine D2 blockade, or leads to other adverse effects such as endocrine disorders. As the name suggests, antipsychotics suppress the psychosis, i.e. the positive symptoms. There is however currently no effective and established medical treatment for the cognitive and negative symptoms although some studies suggest that second generation antipsychotics, especially leponex, would be useful, as may other medication groups such as antidepressants or glycine. No non-pharmacological treatment has been shown to have a dramatic effect on these symptoms domains either. At high doses the side effects of antipsychotics may instead manifest as an increase in the cognitive and negative symptoms making it sometimes difficult for clinicians to assess whether a symptom is an expression of the illness or a side effect of medication. Another problem with treatment which has regained attention in recent years is that a substantial proportion of patients, 10-30%, do not respond to antipsychotics and in this respect are insensitive to therapy.

In conclusion, deeper understanding of the neuroanatomical and neurochemical basis of the negative and cognitive symptoms is needed in order to optimize their pharmacological treatment.

For this reason I chose to focus on the neurochemical regulation of cognitive control in Study 3. If a way to improve cognitive control using pharmaceuticals was found, it could be a potential strategy to affect some of the cognitive symptoms.
1.2.2 Brain Imaging and Schizophrenia

1.2.2.1 The Role of Brain Imaging in the Clinical Context

Towards the end of the 1970s there was great hope that it would soon be possible to diagnose schizophrenia using radiographic methods. The first articles about neuroimaging, showing significant abnormalities in brain morphometry in schizophrenia patients had just been published (63). These were followed by a spate of publications verifying the initial findings, and using refined methods to document more and more types of aberrations.

There are some very promising reports showing that when used correctly, brain imaging could be as important for diagnosis as psychological testing or a thorough status (64, 65). It may also be possible to use brain imaging to differentiate high risk patients that will later develop schizophrenia from those patients that will not (66). However, more critical reviews suggest that this type of study is not designed in a way that renders conclusions that are ready for implementation in clinical praxis (67). It is still the case that the only indication in clinical psychiatry for a brain imaging examination of a patient with suspected schizophrenia is to exclude other causes of the symptoms.

1.2.2.2 Brain Imaging in Schizophrenia Research

The first studies that demonstrated deviations in brain morphometry associated with schizophrenia were also significant in the respect that they irrefutably established schizophrenia as a disease involving the brain. Dilated lateral ventricles were found (63). This stimulated a rapidly increasing knowledge bank about the structural and functional changes in the brain associated with schizophrenia; this knowledge bank constitutes an invaluable contribution to our understanding of the disease. The effects
of the disease on the brain over time can be seen, and the different symptoms domains of the disease can be seen to correspond to different types of brain anomaly.

1.2.2.2.1 Findings Related to Disease Development

At the group level several changes in the brain can be observed in schizophrenia patients (68, 69). An overall decrease in the volume of the parenchyma is seen in the cingulum as well as frontally and temporally in the thinned cortex (69), subcortically, especially in the thalamus (70) and according to some early studies also in the medial temporal lobe structures adjacent to the enlarged ventricles (63). A generally accelerated loss of grey matter compared to healthy aging processes is also seen (71). Using more modern brain imaging methods it has been possible to demonstrate that the disease leads to anisotropy in the pathways connecting different regions of the brain, especially frontotemporally and within the cingulum (72).

Much of this seems to occur at a very early stage of the disease. Even prior to the first psychotic episode, structural changes are present in most patients that are later diagnosed with schizophrenia (73). The temporal lobe has a decreased size both laterally and medially, especially in the upper region. Early in the process the frontal cortex diminishes both laterally and medially, and the cerebral ventricles become enlarged (67, 68, 73). One theory on the consequences of this is that the adjacent areas to affected regions can only to a limited extent compensate for the deficiencies. Functional consequences in the form of imprecise behavioral changes and complex symptomatology may arise because these areas are not specialized for the task (74).

1.2.2.2 Connections to Symptom Domains

The search for neuroanatomical substrates related to particular symptoms of schizophrenia has succeeded in correlating at least some of the symptoms to regional brain areas (16, 75, 76).
1.2.2.2.1 Positive Symptoms

Positive symptoms, which include hallucinations and delusions, are associated with dystrophy in the medial and lateral parts of the temporal lobe (77, 78). These brain regions are involved in the processing of signals from the auditory and visual systems and in the interpretation of the surroundings.

1.2.2.2.2 Cognitive Symptoms

The working memory deficits in schizophrenia are associated with brain abnormalities in dorsal frontoparietal networks (79, 80). The episodic memory impairments are by many authors suggested to reflect medial temporal lobe deficits, with a special focus on the hippocampus (81), while others focus on the association to aberrations in the DLPFC (82). When it comes to impairments in cognitive control, brain imaging studies correlate this to functional aberrations in primarily the ACC (83) and the DLPFC (84, 85), although there are mixed evidence as to whether the activity in these regions is increased or decreased in schizophrenia compared to healthy controls (86).

1.2.2.2.3 Negative Symptoms

Negative symptoms seem to be associated with smaller prefrontal cortex (87). Negative conative symptoms seem to be associated with a regional thinning of the ventromedial prefrontal cortex and the nucleus accumbens, and neurochemically with impaired dopaminergic and glutamatergic systems (88). Negative symptoms have also been correlated several times with anatomical abnormalities in the medial temporal lobe (89-91). The findings in the temporal lobes have however been questioned following the use of more sophisticated examination techniques (92). Since these regions are so critical for affect and socializing some follow-on questions arise: if the volume is normal, what is the functional status of these regions in schizophrenia? Are there correlations between the volume range and the intensity of negative symptoms, or
between the activity level range and negative symptoms? My fourth study explored these questions.

2 MATERIAL, METHODS AND DATA ANALYSIS

In the following section I will describe generally the study populations that have been used, which methods were used for data collection and how the data was analyzed. Due to space constraints I will limit myself to discussion of value for an overall understanding of the work in my thesis. For more details, please see the articles that follow.

2.1 MATERIAL

It has not been possible to answer the questions raised by this research within the framework of a single study only. A total of three collections of data have been used. All were implemented in accordance with the Declaration of Helsinki and all research protocols were approved by local ethical review boards. All persons participating in the study have signed informed consent forms.

2.1.1 The Parachute Project

The first study was conducted using material from The Parachute Project. The Parachute Project is a Swedish multicenter study initiated by Professor Johan Cullberg (93). The study aims to evaluate the effects of a need-adapted treatment model for first episode psychosis (94). The inclusion criteria were recent onset psychosis and the age range of 18-44 years. The exclusion criteria were substance abuse and previous treatment for psychosis. During the period of 1996-1997 a total of 276 recent onset psychosis patients were asked to participate, of which 175 agreed. These patients have now been followed prospectively and longitudinally for over 15 years, with a total
discontinuation of 8%. The 3 year data was complete when I joined the project; I then analyzed this data with regards to diagnostic stability.

Patients had been diagnosed in accordance with DSM-IV. Complementary to regular psychiatric examination and interviews, Structured Clinical Interview for DSM-IV (SCID) questionnaires were used. In order to elicit an optimal baseline diagnosis a review was conducted retrospectively at 12 months, based on all patient information collected up to that time. A new diagnosis was made after 36 months. For 146 patients there were both revised baseline diagnoses and follow up diagnoses. Diagnostic problems were discussed at the annual meetings arranged as a part of The Parachute Project. We were unable to verify whether it was the same psychiatrist making the diagnosis on both occasions or to what extent SCID-1 was also used at the 36 months diagnosis.

2.1.2 Data gathered at the Karolinska University Hospital Huddinge

Studies 2 and 3 are based on data collected at the Karolinska University Hospital in Huddinge. These studies have taken the greater part of my time during my doctorate studies as I have been involved in the entire process, from discussions about the study design and hypotheses to data collection, analysis and writing articles. The initial intention was to include both patients and controls in greater numbers than eventuated. In the end we settled for 11 healthy subjects. The inclusion criterium was the age range 18-44 years. The exclusion criteria were psychiatric or neurological illness, substance abuse or contraindications for MRI such as metallic implants or claustrophobia. Subjects were interviewed to obtain a medical history, handedness was investigated with the Edinburgh handedness scale and the presence of any symptoms of substance abuse or psychopathological symptoms was evaluated with the help of AUDIT, DUDIT and SCID-1.
2.1.3 Thematically Organized Psychosis Study

Through collaboration with Professor Ingrid Agartz I had the opportunity to access data from the ongoing multicenter Thematically Organized Psychosis (TOP) Study, a collaborative study involving the University of Oslo and all of the hospitals in the Oslo region. TOP had been underway since 2004, several years prior to my involvement, so my analysis is based on data collected by others. The clinical participants were recruited continuously from psychiatric clinics (outpatient and inpatient) in four major hospitals in Oslo. Trained psychiatrists and clinical psychologists carried out clinical assessments. Diagnosis was based on SCID interview and set in line with DSM-IV. Information from follow-up visits was used to secure correct diagnoses. Symptoms were rated using the Positive and Negative Syndrome Scale (PANSS). The healthy controls were randomly selected from national statistical records from the same catchment area and contacted by letter to invite them to participate. The inclusion criterium was the age range 18-65 years. Exclusion criteria were hospitalized head injury, neurological disorder, mental retardation. The healthy control subjects were excluded if they or any of their close relatives had a lifetime history of severe psychiatric disorder, if they had an unstable medical condition known to interfere with brain function or if they had a substance abuse or dependency in the last three months. My material includes 28 patients with schizophrenia, the first individuals recruited to the study, and 28 healthy controls.

2.2 METHODS

2.2.1 Calculation of Diagnostic Stability (DS)

DS was calculated in Study 1. It was defined as the degree to which an original diagnosis is confirmed at follow-up (46, 95). I proceeded from how many patients
received the same diagnosis at the 36 months revised baseline and divided by the number of patients with that diagnosis at the revised baseline.

2.2.2 Magnetic Resonance Imaging (MRI)

Firstly, a conceptual overview of the principles behind MRI (96):

Protons such as hydrogen, which is a component of water and thus present in large amounts in the body, rotate around their axle because of thermal energy, and give rise to a magnetic field. This characteristic of protons is called spin. The orientation of the axis of this magnetic field is random, so for example in a biological tissue the protons’ magnetic fields balance each other out so there is no overall magnetic field. When the atoms are placed in a strong external magnetic field however, this is altered. Such a field can be induced by an MRI scanner. The atoms then align themselves so that their axes are oriented along the magnetic field. The majority point in the same direction as the external magnetic field, since this means a low-energy state for the atom, while a minority are oriented in the opposite direction, and take a high-energy position. If energy is applied to the nuclei at a particular frequency known as the resonant frequency, some low-energy nuclei will absorb energy from the system and change to the high-energy state. As a consequence the longitudinal magnetization is converted into transverse magnetization. This is known as excitation. Once the energy source is removed, some nuclei will return to the low-energy state by releasing that energy, which restores the longitudinal magnetization. The emitted energy provides the MRI signal data that later constitutes the MRI images. The changes in the MR signal over time are known as relaxation. There are two types of relaxation: recovery of the longitudinal magnetization (T1*) and decay of the transverse magnetization (T2). By specifying a pulse sequence that targets one of these relation parameters, images can be collected that show different properties of the examined biological tissue.

MRI technique is used in articles 2, 3 and 4 for brain imaging of the research subjects.
2.2.2.1 Functional MRI (fMRI)

BOLD (Blood oxygen dependent) fMRI is a technique introduced at the beginning of the 1990s. It aims at capturing the hemodynamic response to neural activity. There is always a certain level of basic activity in brain tissue, and thus a constant consumption of energy - oxygen and glucose - and a constant refilling with fresh energy from the surrounding blood arteries that pump oxygenated blood from the heart. When a region of the brain is working more intensely, such as the motor cortex does when performing complex movements, or the ACC and DLPFC when exposed to a cognitive conflict situation, more energy than usual is consumed in the region, not least due to the postsynaptic consequences of a neurotransmitter binding to a receptor. An automatically regulated function in the cerebral blood arteries is then activated, which increases the blood flow to areas requiring more energy. Thus, an increase in activity and energy consumption in a region results in dilation of the vasculature of that region. The flow of blood is however ample, and there is soon an excess of new oxygen rich blood. The BOLD fMRI technique takes advantage of this effect, as oxygen rich blood and oxygen depleted blood have differing magnetic properties. Oxyhemoglobin is diamagnetic while deoxyhemoglobin is paramagnetic. The proportion of deoxyhemoglobin decreases when fresh blood flows in. For BOLD fMRI a variant of T2 relaxation is used (T2*) since it is good at detecting local inhomogeneity in the magnetic field such as those due to a changing blood flow in a certain region. Since deoxyhemoglobin reduces the MRI signal, a decrease in deoxyhemoglobin increases the MRI signal. The difference may be as large as five percent. The peak is reached after a few seconds, depending on the type of stimulus and the brain region involved. The signal then decreases and goes into a prolonged undershoot, and finally returns to the baseline value. By studying the anatomic variations during performance of various neuropsychological tests, it is possible to gain an understanding of which regions of the
brain are involved in the function being tested. There is also a correspondance between the amplitude of the BOLD fMRI signal and the amount of neural activity, which makes it possible to compare the activity of a brain region in different experimental situations.

The neuropsychological test performed in the MRI camera by the research subjects is called a paradigm. I have worked with several paradigms during my doctoral period: N-back, counting Stroop and affective counting Stroop, Face Matching Task, finger tapping and imagery finger tapping. I have also designed a paradigm for affect induction on my own using IAPS images. I will now go through those included in the papers that comprise this thesis in more detail - the Stroop tasks and the Face Matching Task.

2.2.2.1.1 The Stroop Task Paradigms

The classic Stroop test (97) (named for its inventor) involves a task where a series of words are to be read aloud. The subject is to read as fast as possible, but without making mistakes. The words denote colors. The problem, or distraction, is that the ink used to write the word is of a different color to that named by the word. For example, the text may read “RED” but be written in blue. The Stroop effect is that these words are read a little slower than when the word “RED” is written in red ink, and that the reader more often makes mistakes reading words written in the “incorrect” color.

It is considered that the Stroop test examines the subject’s cognitive control, his or her ability to continue targeted behavior despite the distraction. The Stroop test is also available in a version adapted for MRI examinations. The task in the MRI version is to state the number of copies of a word shown at one time on a screen. There may be between one and four copies of the same word. The word is at times neutral, such as “TABLE” or “CHAIR”, and at other times it is a distracting ("interfering") word such as a counting word (“ONE”, “TWO”, “THREE” or “FOUR”) which does not
correspond to the correct answer for the task. The text may read “FOUR FOUR
FOUR”, which is confusing because the correct answer is three. This paradigm is called
counting Stroop (cStroop) and was developed by Bush et al (98).
A further version of the test has been developed by the same research group that
designed cStroop - a Stroop test which captures the capacity for cognitive control in the
presence of affective distracting stimuli. This test is called the affective counting Stroop
(aStroop) (99). The format is the same as for cStroop but instead of numerals,
emotionally charged terms such as “DEATH”, “HAPPINESS” and “ORGASM” are
used.
It has been repeatedly demonstrated that schizophrenia patients perform worse than
average in the Stroop test (84, 100). This applies to both superimposed cognitive
problems such as cStroop with numerals, or to simultaneous affective induction, as
with affectively charged words or images in aStroop. This is linked to impaired
cognitive control which is a central neurocognitive feature of the disease.

2.2.2.1.2 The Face Matching Task Paradigm
The Face Matching Task Paradigm involves looking at pictures of people who exhibit
different affects (101). During this time the reactions of the test subject are noted - their
facial expression, pulse, blood pressure, skin conductance - i.e. various peripheral affect
markers. Approximately the same regions of the brain involved in producing the affect
as the person in the photo, are activated in the person looking at the photo. This
phenomenon is called neural resonance (101). Face Matching Task Paradigm is
designed to activate the amygdala regions in particular.

2.2.2.2 Pharmaco fMRI
Pharmacological MRI (phMRI) is an increasingly used method, in which fMRI is used
in conjunction with a pharmacological probe (102). In this way, phMRI permits non-
invasive in vivo mapping of large-scale physiological or neurocognitive properties of centrally active compounds. This opens up for greater insights into transmitter-related modulation of large-scale neurocognitive systems (103).

I used three different pharmacological probes during work with the thesis: bupropion, haloperidol and escitalopram, and studied their effects på N-back, affective induction, cStroop and aStroop. In the third article we present the results of the combination of escitalopram and cStroop as well as aStroop. Serotonergic probes have previously been used to measure the involvement of 5-HT in various neurocognitive functions (26) but we are not aware of earlier studies using SSRIs in combination with cStroop and aStroop in healthy subjects.

2.3 DATA ANALYSES

2.3.1 Diagnostic Stability

DS was calculated for each diagnosis and diagnosis group (i.e. the schizophrenia spectrum group, the affective psychosis group and the miscellaneous psychotic disorders group).

2.3.2 MRI - Volumetrics

In all MRI related analysis the same software package, the FSL software (FMRIB Oxford) was used for data analysis.

As an anatomical map to place the results of the calculation of BOLD data, we produced an averaged image of each study population’s brains from Studies 2, 3 and 4. A T1-weighted anatomical image (MP-RAGE) was acquired for all subjects. They were subsequently averaged together, after rigid-body registration.

A comparison between the amygdala volumes of schizophrenia patients and healthy controls was made in Study 4. The volume was calculated using T1-weighted images. FIRST 1.2 was used for automatic segmentation of the amygdala (104). In FIRST the
outline of the amygdala has a default setting from 336 manual tracings that provide a
starting point for the automated segmentation. We used FIRST to compute meshes
representing the volumetric outputs. We applied boundary correction that further
refined the delineation of the amygdala. We calculated intracranial volumes and
derived a scaling factor for each participant using SIENAX. The scaling factor was
derived from the difference in size of each individual brain in relation to the MNI152
standard brain. We used this scaling factor to normalize all volumetric measures in each
subject.

2.3.3  fMRI

Functional MRI was used in Studies 2, 3 and 4. Data processing was carried out using
FEAT (FMRI Expert Analysis Tool), part of FSL (105). The approach was in principal
the same for all three.

2.3.3.1  Preprocessing

Our starting material was the BOLD sensitive T2*-weighted echo planar images. Each
image consisted of a number of axial slices covering the whole brain. The images were
oriented to standard space MNI152 using FLIRT (106) and motion corrected using
MCFLIRT (107). The non-brain tissue was removed by the Brain Extraction Tool
(BET) (108). Spatial smoothing was performed using a Gaussian kernal. To account for
time difference in slice acquisition, we performed slice-timing correction using Fourier-
space time-series phase shifting. Grand-mean intensity normalization of the entire 4D
dataset was achieved by a single multiplicative factor.

2.3.3.2  First Level Analysis

The parameter estimates (PE) for all voxels were calculated using a general linear
model (GLM) and contrast imaging (COPE) comparing the task condition with the
non-task condition. The time-series statistical analysis was carried out using FILM
(FMRIBs Improved Linear Model) with local autocorrelation correction (109). Clusters were determined by $Z>2.3$ and a corrected cluster significance threshold of $p=0.05$. The result was corrected for multiple comparisons.

A region of interest analyses into restricted sets of voxels was also performed using the same approach. The anatomical spread of the areas (Studies 2 and 3: ACC and middle frontal gyrus used as a proxy for DLFPC, Study 4: amygdala) was defined by the Harvard-Oxford cortical anatomical atlas supplied with FSL.

2.3.3.3 Higher Level Analysis

Higher level analyses in which groups of images were compared with each other were carried out using FLAME (FMRIB’s Local Analysis of Mixed Effects) stage 1 + 2 (110-113). $Z$ (Gaussianized T/F) and statistic images were thresholded using clusters determined by $Z > 2.3$ and a (corrected) cluster significance threshold of $p = 0.05$.

In Study 4 we included age, gender and current use of antipsychotics (Y/N) medication as covariates in our regression model.

2.3.3.4 Pharmaco fMRI

Analysis of pharmaco fMRI data does not involve any difference of principle in relation to the method described in the paragraph above. Each subject’s activation before and after medication was compared using a paired T-test in a mixed effect analysis (FLAME 1 and 2). Cluster forming threshold was set at $Z > 2.3$ and a cluster significance threshold of $p = 0.05$ (corrected).

3 RESULTS

3.1 Diagnostic Stability in First Episode Psychosis

At revised baseline, 41% of patients had a schizophrenic spectrum diagnosis, 15% affective psychosis and 43% another type of psychosis diagnosis (figure 2).
At 36 months, 34% retained the exact same diagnosis as at revised baseline. We found that the DS differed between the different diagnoses and diagnosis groups. The highest level of stability was found for schizophrenia (DS 83%) and the schizophrenia spectrum group (DS 73%). There was a remarkably low DS for delusional disorder (33%) and schizoaffective disorder (30%). Finally, it was observed that although a change

![Figure 2: Diagnosis (DSM-IV) at revised baseline and at 3-year follow-up in a total group of first-episode psychosis patients (n=146) in the Swedish Parachute Project.](image)
in diagnosis within the groups was frequent, the flow of patients between the groups was low. Those patients leaving the groups in this study seemed mostly to be those patients that recovered.

3.2 NEURAL CORRELATES OF COGNITIVE CONTROL

We observed, as expected, a significant rostrocaudal distinction in the medial PFC/ACC similar to that described by Bush and Whalen et al. (99, 114). We also found statistically significant differences in the lateral PFC, namely, rostrocaudal and dorsoventral distinctions in the lateral PFC including Brodmann areas 9 and 46 with aStroop preferentially activating rostral and ventral parts and cStroop preferentially activating caudal and dorsal aspects of lateral PFC (figure 3).

Figure 3. BOLD signal activations during aStroop and cStroop in the ACC and the DLPFC. The upper panel shows comparisons of interference and neutral tasks (incongruent>neutral) for aStroop (red-yellow) and cStroop (blue-green). Left and right are shown according to radiological convention.
3.3 NEUROCHEMICAL REGULATION OF COGNITIVE CONTROL

The ACC and DLPFC were activated by aStroop and cStroop both before and after intake of 10 mg of escitalopram. After intake, the BOLD signal in the rostral ACC was decreased in the aStroop contrast (aStroop > cStroop, corrected p < 0.05), and left intact in the dorsal ACC and DLPFC for the cStroop contrast (cStroop > aStroop, corrected p < 0.05). When the effects of escitalopram were quantitatively compared, the rostral ACC during aStroop turned out to be significantly more activated before compared to after drug intake (corrected p < 0.05). The peak voxel (x, y, z: 6, 44, 12) survived a corrected threshold of p < 0.05 (at the voxel level, using Gaussian random field theory) (figure 4). The difference was primarily driven by the aStroop after > before escitalopram contrast (figure 5). No other significant difference was noted in the effects of escitalopram in medial or lateral PFC.
Figure 4. Picture A) and B) shows brain activation during affective counting Stroop (aStroop) and cognitive counting Stroop (cStroop), before (controls) and after intake of escitalopram (cluster forming threshold $Z \geq 2.3$, corrected $p=0.05$, MNI $z=29$). In both Stroop conditions there are significant activations in anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex, key nodes in the neural cognitive control networks. Picture C) shows in a region of interest analysis of the ACC, where aStroop activates more than cStroop before compared to after drug intake. For display purposes the cluster shown in the image has an uncorrected threshold of 0.005, but the peak voxel ($x, y, z: 6, 44, 12$) survived a corrected threshold of $p<0.05$ (at the voxel level, using Gaussian random field theory).
Figure 5. The BOLD percentage changes in the right rostral anterior cingulate cortex for affective counting Stroop (aStroop) and cognitive counting Stroop (cStroop) before and after intake of escitalopram. The differences were not statistically significant. The mask was smoothed with a gaussian kernel set to 1.5 mm, surrounding the peak voxel shown in figure 2A (x, y, z: 6, 44, 12).
3.4 NEURAL CORRELATES OF NEGATIVE SYMPTOMS

In our patient group we found a statistically significant and negative correlation between blunted affect and left amygdala activation during presentation of positive affect (Spearman’s rho -0.5177, p = 0.0048) (figure 6). We also found that right amygdala volume predicted stereotyped thinking, another negative symptom of schizophrenia (p = 0.043; adjusted for age, gender and treatment with antipsychotics) (figure 7).

We did not find a statistically significant group effects on amygdala volumes or BOLD fMRI results during the tasks.
Figure 6. Correlation between emotional blunting (PANSS, item N1) and COPE values in left amygdala of SZ subjects, dotted lines demarks 95% confidence interval.

Figure 7. Correlation between stereotyped thinking (PANSS, item N7) and volume of right amygdala (dotted red line demarks 95% confidence interval, blue line demarks mean value of right amygdala size).
4 DISCUSSION

4.1 DIAGNOSTIC STABILITY IN FIRST EPISODE PSYCHOSIS

We performed a descriptive study of DS in a group of 175 patients in first-onset psychosis that were followed prospectively and longitudinally. We found that the diagnostic stability among the different psychotic disorders varied greatly and that schizophrenia and the schizophrenia spectrum group had high DS, while others such as delusional disorder and schizoaffective disorder had low DS.

The findings are in agreement with previously published literature. The remarkable finding in our study is not the high diagnostic stability of the schizophrenia group, but rather that some other diagnoses have such a low DS. It is especially notable for schizoaffective disorder and delusional disorder, two diagnoses associated with such a long disease process that the diagnoses should be present at a three year follow-up. In the case of other diagnoses the results are more difficult to evaluate – short, transient psychosis and schizophreniform disorder are two diagnostic entities for which the criteria in DSM-IV state that the duration is not to exceed 1 or 6 months respectively. It may have been possible to better capture the diagnostic stability for these diagnoses if the baseline diagnosis was compared with the revised baseline diagnosis.

An explanation of the finding that delusional disorder and schizoaffective disorder have such a low DS over three years may be the concept that McGorry calls the inherent process of psychotic diseases (48). This states that the disease tends to initially be of a diffuse and fluctuating character, but that it stabilizes and becomes more distinct over time. In other words, the patient may have been assessed during an indistinct phase, resulting in misinterpretation and an incorrect diagnosis. A further contributing factor may be the format of DSM-IV and ICD-10. The criteria and usability of these classification systems are not adapted for use in first episode cases; instead they tend to
characterize patients in a stable phase of the disease. I think this is a deficiency in the classification systems as the importance of reliable diagnostic criteria is extra important in the initial phase of the disease.

We conclude that schizophrenia is a certain diagnosis to use even in the early stages of the disease, however the certainty is questionable for some of the other psychotic disorders.

In the article we suggest a method of increasing the diagnostic stability, namely to be more general in the initial diagnosis and only use group diagnosis terms: schizophrenia spectrum, affective psychosis and psychotic disorder NOS respectively. A more specific diagnosis can be made when there is enough information. Using this approach would minimize the risk of patients receiving a diagnosis that required review at a later point.

In future studies, it would be interesting to study predictors for various prognoses in schizophrenia and within the spectrum of schizophrenia – perhaps there are ways to further increase the diagnostic accuracy for that group.

4.2 NEURAL CORRELATES OF COGNITIVE CONTROL

In this fMRI study where 11 healthy control subjects performed the cStroop and the aStroop in one session we found that the key regions in the cerebral networks for cognitive control were activated, however it was not only ACC that demonstrated a functional subdivision into a dorsal cognitive and a rostral affective area, but DLPFC did also.

Although the DLPFC is not known to have been studied in this way previously there are plenty of other studies that found functional subdivisions in the PFC (115-117) and in the DLPFC in particular (84). Although dissenting opinions (118) a current model of PFC functional specialization supports the notion that affective stimuli would
preferentially activate ventral parts of the PFC, while cognitive paradigms activate more dorsal and lateral parts (119). Our findings are therefore not unreasonable.

If these observations were to be reproduced it would be of interest for many reasons, including clinically: to understand the structure of the prefrontal cortex, an area of the brain which has numerous and complex functions in the higher mental faculties; in the interpretation of localized lesions in the lateral PFC; and in the understanding of cognitive control.

Unfortunately this study is weakened by a number of flaws which means that findings must be interpreted with caution. The main flaw is that the number of subjects is small, so the external generalizability is decreased. Furthermore, behavioral data is lacking due to technical problems with the hand held button device. This means that it is not certain whether there actually was a Stroop effect or whether the level of difficulty of the various paradigms were calibrated in relation to each other. We now see the activity in the key regions for cognitive control and, since none of the subjects reported any problems with the implementation, we interpret this as meaning that a cognitive control situation was actually present. It cannot however be excluded that aStroop is an easier task than cStroop and that the gradient in the DLPFC is instead related to the degree of difficulty. Reaction time and correct/incorrect response data would have been able to rule this out.

Our conclusion is that both tests seem to activate different areas of the DLPFC and we assume that this is related to the different circuits of the cognitive control network which are involved in cognitive control, those for the distractions of a cognitive and affective nature respectively.

In future studies it would be interesting to compare healthy subjects with patients diagnosed with diseases that are known to be associated with impaired cognitive control, such as schizophrenia. This would allow further exploration of this aspect of
functional neuroanatomy and potentially contribute to understanding of the disease state.

4.3 NEUROCHEMICAL REGULATION OF COGNITIVE CONTROL

In this experimentally designed fMRI examination of 11 healthy control subjects that performed the aStroop and cStroop before and after the intake of 10 mg escitalopram, a selective serotonin reuptake inhibitor, we found that the activity in the rostral ACC decreased significantly more for aStroop than for cStroop. It appears that practicing cognitive control in response to affective conflict does not result in as much activity in the rostral ACC following intake of an SSRI. As named in the introduction, similar studies have been conducted previously where the availability of serotonin in the synapse has been decreased instead of increased, by use of tryptophan depleted diet. The reverse has then been observed, that activity in the ACC increased for aStroop (27). In light of this, our findings are plausible. This localization of activity is reasonable as ACC has a known functional subdivision in which the rostral part is more affective in character and the dorsal part is more cognitive (120). Furthermore, it is also the case that the rostral area is more innervated by serotonin than the cognitive area (121); it follows that the effect of SSRIs should be greater in this region.

An interpretation that we favor is that escitalopram by reducing the impact of negative emotions on brain activity made the burden of the affective interference less demanding.

Unfortunately this study has some deficiencies and the results must be interpreted with caution. A placebo group was lacking. We made an assumption that the placebo effect would be the same for aStroop as for cStroop and that a placebo group therefore would be redundant, but this is not necessarily the case. Furthermore, there is no control of order in which tasks were performed, which makes it difficult to know what is an effect
of the SSRI and what is an effect of training. It is possible that the training effect is
greater for the processing of affective conflicts than for cognitive conflicts. In addition,
no behavioral data is available due to technical problems with the hand held button box.
This makes interpretation of the altered BOLD values more doubtful.
Our conclusion is that suppression of the activity in the rostral region of the ACC in the
second session is significantly greater for aStroop than for cStroop and our
interpretation is that SSRIs have contributed to this phenomenon.
It would be interesting to test this hypothesis in a more well designed study, which
would include a placebo group, crossover design and a greater number of study
subjects. It would also be interesting to have research subjects exposed to SSRI
preparations for the length of time that is required for clinical effect in the treatment of
depression, in order to make the study more clinically relevant. Furthermore, it would
be interesting to compare healthy subjects with schizophrenia patients to see whether
SSRI preparations could help patients exercise cognitive control despite affective
distractions such as anxiety or paranoid ideas. This study suggests that SSRI
preparations may be able to improve cognitive control for distractions within the
affective domain.

4.4 NEURAL CORRELATES OF NEGATIVE SYMPTOMS

In this, the fourth and final study of the thesis, we studied the role of amygdala volume
and activation patterns in the degree of negative symptoms by comparing 28
schizophrenia patients' structural and functional MRI images with as many healthy
control subjects. Within the schizophrenia group the extent of negative symptoms
correlated with both the volume and the activity of amygdala, however we found no
statistically significant differences between the patient and control groups as regards to
the volume or level of activity as measured by BOLD fMRI.
We interpret the fact that both the volume and the activity of amygdala correlate with the extent of negative symptoms as showing that the amygdala is indeed involved in the emergence of negative symptoms. That there is no difference in volume between the groups is in line with the findings of a large well-designed study of recent years (92). We found no difference between the groups in regard to the BOLD value for task compared to non-task for the Face Matching Task paradigm. It has been found that studies using low-level baseline, as we have done (geometric figures), showed no significant difference between healthy individuals and schizophrenia patients. However, a difference can be seen when a high-level baseline is used, i.e. where the same type of stimulus is used but without affect (which would have corresponded to neutral faces in our study). It is thus likely that the anomaly with regard amygdala activity in schizophrenia lies in the regulation of basal activity rather than the regulation of task activity.

We conclude that both the volume and function of the amygdala correlate to the negative symptoms of schizophrenia, but that neither the volume nor the BOLD activation of the amygdala themselves differ between schizophrenia patients and healthy persons.

In future studies it would be interesting to study whether the amygdala’s volume and activation pattern correlate to the corresponding characteristics in the healthy, such as social ability or the capacity to reason in a free and unrestrained manner. In this case it would contribute to our knowledge of the amygdala’s function. Further, it would be of interest to study the different nuclei of the amygdala with a higher resolution MRI camera. There may be structural and functional differences at a level that the 1.5 T MRI scanner used in this experiment was not able to differentiate.
5 CONCLUSION

Schizophrenia is among the world’s top ten causes of long-term disability and as such places a heavy illness burden on the affected individuals and an equally heavy socio-economic burden on society. Currently our understanding of the disease is incomplete, and our treatment options are far from optimal.

Understanding the neuropsychology, neurochemistry, and the neuroanatomical substrates of complex brain functions like cognitive and affective processing may help explain, and ultimately prevent or improve the treatment of major clinical psychiatric conditions such as schizophrenia.

It remains to be seen whether the results of this research project will contribute in an enduring way to the overall puzzle that is schizophrenia. However, on a personal level, as far as the doctorate studies in general are concerned, I feel convinced that this thesis is the first step on a long journey as I continue further in to the world of psychiatric research.

Koh Samui, 27 June 2013
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