Physiological Aberrations in Patients with Schizophrenia

BJÖRN NILSSON
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Abstract

In schizophrenia, subtle aberrations in the brain cause functional disturbances like psychotic symptoms and social disability. There are, however, also disturbances outside the CNS indicating a systemic manifestation in the disease. The aim of the present thesis was to gain deeper understanding of the pathophysiological mechanisms underlying schizophrenia with a particular interest in peripheral and systemic manifestations with relevance for the increased risk of obesity and metabolic complications seen in the disease. Therefore, resting energy expenditure (REE), physical capacity, and relevant body composition variables were measured in patients with schizophrenia and in healthy controls. Also niacin skin flush response and electrodermal activity (EDA) were studied.

Patients with schizophrenia exhibited significantly lower REE expressed as kJ/kg, and also lower values compared with predicted levels than the controls. The difference could not be attributed to medication or variations in body composition between the two groups. There was a gender difference with the lowest levels found in male patients.

Male patients exhibited significantly lower physical capacity in terms of predicted maximal oxygen uptake capacity and faster increase in respiratory quotient than male controls.

The oral niacin test revealed a significantly delayed skin flush reaction in patients compared with controls. The patients also exhibited lower EDA response. There was a significant association in response patterns for the niacin and the EDA tests in the patients, but not in controls.

In a test-retest study in patients there was acceptable stability for EDA measures but low test-retest stability for niacin variables. The previously found association in responses for the two tests was, however, replicated.

The results gain support for the concept of schizophrenia as a disease with systemic manifestations including metabolic dysregulation. The findings add to the understanding of the weight gain and the increased risk for cardiovascular morbidity seen in this condition.

Keywords: Schizophrenia, resting energy expenditure, body composition, physical capacity, oxygen uptake capacity, respiratory quotient, niacin, skin flush reaction, electrodermal activity

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urn:nbn:se:uu:diva-9521 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-9521)
“Omnia mutantur, nihil interit” Ovidius, Metamorphoses
Everything changes, nothing perishes

To Martin and Saga
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


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### Abbreviations

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<th>Definition</th>
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<tbody>
<tr>
<td>AA</td>
<td>Arachidonic acid</td>
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<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
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<td>BF</td>
<td>Body fat</td>
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<td>BIA</td>
<td>Bioelectrical impedance analysis</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<td>BMR</td>
<td>Basal metabolic rate</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
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<td>CVD</td>
<td>Cardiovascular disease</td>
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<td>D2</td>
<td>Dopamine 2 receptor</td>
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<td>DHA</td>
<td>Docosahexaenoic acid</td>
</tr>
<tr>
<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders version IV</td>
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<tr>
<td>EDA</td>
<td>Electrodermal activity</td>
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<tr>
<td>EPA</td>
<td>Eicosapentaenoic acid</td>
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<td>EPS</td>
<td>Extrapyramidal side effects</td>
</tr>
<tr>
<td>FAO/WHO/UNU</td>
<td>Food and Agriculture Organization / World Health Organization of the United Nations University</td>
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<tr>
<td>FFM</td>
<td>Fat free mass</td>
</tr>
<tr>
<td>FM</td>
<td>Fat mass</td>
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<tr>
<td>ICD-10</td>
<td>International Classification of Diseases and Related Health Problems, tenth revision</td>
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<td>ICW</td>
<td>Intracellular water</td>
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<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<td>MRS</td>
<td>Magnetic resonance spectroscopy</td>
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<tr>
<td>Na⁺K⁺ATPase</td>
<td>Sodium potassium ion transporter enzyme</td>
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<tr>
<td>NMDA</td>
<td>N-methyl D-aspartate receptor</td>
</tr>
<tr>
<td>NSF</td>
<td>Non-specific fluctuations</td>
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<tr>
<td>PANSS</td>
<td>Positive and negative syndrome scale</td>
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<td>PET</td>
<td>Positron emission tomography</td>
</tr>
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<td>PGD2</td>
<td>Prostaglandin D2</td>
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<tr>
<td>PLA2</td>
<td>Phospholipase A2</td>
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<tr>
<td>PUFA</td>
<td>Polyunsaturated fatty acids</td>
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<tr>
<td>REE</td>
<td>Resting energy expenditure</td>
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<tr>
<td>RMR</td>
<td>Resting metabolic rate</td>
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<tr>
<td>RQ</td>
<td>Respiratory quotient</td>
</tr>
<tr>
<td>SCL</td>
<td>Skin conductance level</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>SCR</td>
<td>Skin conductance response</td>
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<tr>
<td>SGA</td>
<td>Second generation antipsychotic</td>
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<tr>
<td>TEE</td>
<td>Total energy expenditure</td>
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<tr>
<td>VO\textsubscript{2max}</td>
<td>Maximal oxygen uptake</td>
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<tr>
<td>WFFM</td>
<td>Water in fat free mass</td>
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Introduction

The concept of schizophrenia

Schizophrenia is a heterogeneous syndrome with a highly variable clinical picture, premorbid adjustment, course and outcome. The question has therefore been posed as, whether schizophrenia is a single entity or a cluster of different pathogenetical conditions with a fairly similar phenotype.\textsuperscript{1, 2} Bearing this heterogeneity in mind, schizophrenia is nevertheless a quite common and often chronic disease necessitating life-long treatment. In many cases schizophrenia is a severe disorder with devastating consequences for the affected individual. The need for rehabilitation and care is consequently great, and schizophrenia represents one of our most important public health problems, incurring large health care costs.

The disorder has a global distribution across national, cultural and socio-economic boundaries. The lifetime risk for schizophrenia is often cited as being quite constant, slightly below 1% worldwide. Contrary to earlier beliefs, this figure does show at least a threefold variation in different studies and has probably been overestimated in the literature.\textsuperscript{3, 4} Another long-standing conviction is that the incidence rate for the disease is the same for men and for woman, when in fact men seem to be at somewhat higher risk.\textsuperscript{5, 6} In 1991 a prevalence assessment in a Swedish catchment area was performed, and prevalences of 0.42% and 0.33% were found in males and in females, respectively.\textsuperscript{7} In Sweden it is currently estimated that about 35 000 people are suffering from the disease.

Schizophrenia is generally considered to be a nervous system illness and the most striking symptoms are undoubtedly related to the higher functions of the brain. However, a number of publications have also revealed a broad spectrum of aberrations also outside the central nervous system, and some researchers look upon schizophrenia as a systemic disease.\textsuperscript{8, 9}
The clinical picture

Diagnostic dilemmas

Psychosis is often described as a condition involving loss of contact with reality. This is a common sign in schizophrenia, but it is also seen in several other psychiatric conditions like dementia, mania and psychotic depressions. The specific psychotic symptoms typically seen in schizophrenia, such as hallucinations and paranoid ideation, may also occur in a large variety of conditions like post-traumatic stress disorder, substance abuse, personality disorders, and may even occur subclinically in the normal population. At present, there is neither a single clinical symptom nor any laboratory, radiological, psychological or other conceivable marker that is specific for schizophrenia. Thus, schizophrenia may represent disturbances in many aspects of behaviour, cognition and emotions, and the diagnosis is based on a combination of different features. The current fourth version of the diagnostic statistical manual (DSM-IV) requires two of five characteristic symptoms for diagnosis. In addition to the symptom criterion, five additional prerequisities must be fulfilled; one that is particularly noteworthy is a social or occupational dysfunction. DSM-IV requires a duration of at least six months regarding signs of illness, while the International Classification of Diseases and Related Health Problems; 10th Revision (ICD-10) has a broader definition requiring only a one-month duration for diagnosis.

Originating from Kraepelin and Bleuler, DSM-IV also uses the subdivisions of paranoid, disorganized, catatonic, undifferentiated and residual types of schizophrenia. These subtypes may be relevant for the understanding of a specific clinical picture, but they have proven to be of less value for research purposes. Schizophrenia symptoms may also vary over time and in relation to different medication strategies, and the interface and interaction with affective symptoms or other psychiatric conditions are not always obvious. Schizophrenia is thus a complex syndrome and proper diagnostic criteria are still being debated.

Psychotic symptoms have intrigued physicians and researchers for centuries. An early subdivision into explicit symptoms and more withdrawal-related symptoms was proposed by the British neurologist Hughling Jackson in 1894. Two pioneers in schizophrenia research, Kraepelin and Bleuler, considered what are now called cognitive and negative symptoms to be the core characteristics of schizophrenia. Emil Kraepelin identified several features of the schizophrenia complex, among them poor premorbid adjustment, early onset, “negative” symptoms and poor prognosis. He used the expression “Dementia Praecox”, which implied a neurodegenerative course. Somewhat later, Eugene Bleuler focused on the autistic and cognitive features of the disease. He used the term schizophrenia and proposed the core symptoms to be autism, ambivalence, and affect and association distur-
bances. In contrast Schneider placed great emphasis on classic positive - first rank - symptoms. Schneider’s thoughts have strongly influenced the operational criteria in both the current as well as the preceding versions of DSM. In one sense, when a distinction between type I and type II schizophrenia syndromes was introduced by Timothy Crow, wherein type II resembles a more negative subtype, this could be considered a revival of the theories of Kraepelin and Bleuler. This dichotomising of symptoms had a strong impact on the research and treatment of schizophrenia.

Positive, negative and cognitive symptoms
The current widespread division between two essentially different modes of symptoms, the positive and negative subtype model, originates from Nancy Andreasen. The positive symptoms refer to additions to normal behaviour, such as hallucinations, delusional ideation and disorganised speech or behaviour. Negative symptoms, on the other hand, refer to behavioural deficits such as lack of motivation and emotional response. The diagnosis of schizophrenia according to DSM-IV relies largely on the occurrence of positive symptoms. The more general concept of negative symptoms constitutes only one of the five symptom criteria in DSM-IV.

Hallucinations may be polymodal and originate in perceptual disturbances in any of the five senses, but auditory hallucinations usually prevail in the clinical picture. Independently, or secondary to perceived voices, delusional conceptions may arise that are generally paranoid or persecutory in nature, but megalomaniac delusions are also common. Ideas of reference and magic thinking are frequent and are often found in remission states when actually asked for. Lack of insight may also be present and often implies poor outcome.

The negative symptoms, which seldom present any acute psychiatric problem, constitute the overwhelming challenge in schizophrenia rehabilitation. While the positive symptoms may be passing or treatable, the negative symptoms tend to remain, thereby causing long-term disability, and are thus associated with poor functional outcome. Avolition, the lack of energy, motivation and drive, is often manifest and may produce a never-ending need for repetitive supportive coaching to maintain basal daily activities. In extreme cases the negative symptoms will eventually lead to a chronic deficit state with the patient apparently living on very low jets. In other cases the negative symptoms are represented by anhedonia, apathy, blunted emotions or lack of social interactive skills. The newer generation of antipsychotic medication is thought to have a somewhat better effect on negative symptoms than older drugs, but the problem often remains, and in some cases the medication itself may cause secondary negative symptoms. Negative symptoms are also reported to correlate with biological findings like brain ventricular enlargement and electrodermal activity (EDA).
Cognitive disturbances may be intertwined with negative symptoms and are often discussed with respect to the unfavourable outcome.\textsuperscript{28, 29} Neurocognitive testing will reveal an array of cognitive dysfunctions in schizophrenia such as disturbances in attention, working memory, information processing and executive functions, generating obstacles for stepwise planning and implementation of everyday activities.\textsuperscript{30, 31} Interesting research is underway on possible remedies for cognitive disturbances in schizophrenia both in the form of pharmacological treatments\textsuperscript{32, 33} and psychological programs aimed at cognitive enhancement.\textsuperscript{34, 35} Recently the Board of the National Institute of Mental Health in the US agreed on a standardised test battery - the MATRICS – that was developed primarily for use in such cognitive enhancing remedies.\textsuperscript{36, 37}

Other symptom dimensions: co-syndromality or comorbidity?
The original Kraepelinian distinction between schizophrenic and affective psychoses that survives in current diagnostic manuals has been questioned,\textsuperscript{38} not least in familial and genetic studies. Schizophrenia itself comprises affective disturbances like emotional flattening or inappropriate affects, but patients are also at risk for comorbidity with other affective disorders. Manifest clinical depression is at least as common in schizophrenia as in the general population, and should be diagnosed and treated.\textsuperscript{39} Negative symptoms may sometimes also be mistaken for depression and vice versa. Clinical cases with prominent psychotic and affective symptoms represent a specific problem. The term schizoaffective disorder is used both in DSM-IV and ICD-10 for a separate diagnosis that unfortunately has a rather uncertain quality.\textsuperscript{40} Some patients may show alterations in their clinical picture, with relapses of an affective type despite the lack of such symptoms in the first episode. Familial studies have also shown a broader vulnerability for relatives of schizophrenia probands, with co-aggregation of both affective and psychotic disease.\textsuperscript{41}

The course of schizophrenia
The onset of schizophrenia typically occurs during early adulthood. When diagnosed according to DSM-IV criteria, the disease is found to afflict slightly more males than females.\textsuperscript{5, 6} For females, the age of onset is somewhat later and there are also reports of a small incidence peak during menopause, suggesting a protective role for estrogens.\textsuperscript{42} Female patients have better premorbid adjustment, better response to treatment, and better outcome than males,\textsuperscript{43} and they also show less negative symptoms. Like the clinical picture, the lifetime course of schizophrenia is also highly variable. In some patients the disease is characterised by outbursts of acute positive symptoms followed by longer periods of either a higher level of function or persisting negative symptoms.
Some patients may have a dramatic onset of symptoms but a good treatment response and the capacity to learn how to cope with persisting symptoms, making long-term improvement and even recovery a possibility. In other patients the onset is slow and insidious and the ongoing disease process demands a progressively higher level of support. A minority of patients are refractory to pharmacological treatment and show persisting positive symptoms at any given time point regardless of antipsychotic medication.

There is strong agreement that intervention in schizophrenia should be started as soon as possible. A much cited concept is the duration of untreated psychosis (DUP), which refers to the time from onset of psychotic symptoms to the start of treatment. DUP is thus reported to correlate with outcome.\textsuperscript{44} Much effort has been made to identify high-risk individuals in a prodromal state even before the debut of typical symptoms. Such detection may facilitate prodromal treatment and prevent the transition to manifest schizophrenia.\textsuperscript{45} The problem is to define the more vague prodromal state and differentiate it from other psychiatric morbidity in early adolescence.

Many patients experience symptomatic relief and improved quality of life during the course of schizophrenia. However, despite advances in pharmacological treatment and in rehabilitation strategies, the outcome in terms of functional improvement has remained poor.\textsuperscript{46, 47} The rate of patients who are successfully rehabilitated to independent living and full time work is still low,\textsuperscript{48} and a disability pension is frequently received quite early in the course of an often lifelong disease. Full recovery without the need for medication or support of any kind is seldom possible. A more achievable goal for treatment therefore involves the concept of remission, referring to a state when positive, negative and cognitive symptoms are reduced to a more subclinical level.\textsuperscript{49, 50} Schizophrenia has a higher mortality compared to that in the general population.\textsuperscript{51, 52} A schizophrenic illness with substantial negative symptomatology inevitably results in profound alterations in daily activities. A sedentary indoor lifestyle with a lack of physical exercise, an unsatisfactory diet and excessive smoking habits are often seen. Many patients are consequently prone to develop cardiovascular and respiratory problems and other somatic comorbidity. On the whole, the predicted life span for a patient with schizophrenia is considerably shorter than in the general population,\textsuperscript{52} and a major cause is cardiovascular disease.\textsuperscript{53}

**Etiology**

A search of the PubMed database on 1 august 2008 for “schizophrenia” revealed 80265 scientific publications. It is evident that there is vast knowledge about the disease regarding its epidemiology, neurochemistry and treatment. However, major questions about the cause and pathophysiology of schizophrenia are still unanswered.
Genetics

It is estimated that genetic factors contribute to approximately 80% of the disease process. This strong heritability does not contradict the fact that the majority of clinical cases occur sporadically. Siblings of probands have about a 10-fold risk of developing schizophrenia, while the offspring of one schizophrenic parent have a slightly higher risk. If both parents have schizophrenia, the risk is considerably higher. A monozygotic twin with an affected proband has about a 48% risk of developing schizophrenia. These increases in risk can be compared to the general population lifetime risk of approximately 0.7%. Paternal age also contributes to the risk for both schizophrenia and bipolar disorder. From these facts it is obvious that schizophrenia is a disease with a strong genetic etiology, while environmental or epigenetic factors nevertheless play an important role for the development of the disease. The mode of genetic transmission in schizophrenia is still unclear, but a polygenic threshold model has had strong support for a long period of time. Thus a number of common gene polymorphisms at different loci may be involved that are necessary for disease development but each of which is weakly penetrant or has a modest effect. This view is in contrast to recent interesting findings and hypotheses regarding rare but highly penetrant novel DNA variations.

Linkage and association studies in schizophrenia have a long and often disappointing history. Many susceptibility loci have been reported but the findings have sometimes been hard to confirm in subsequent studies. Nevertheless, during the past decade several probable genetic markers of vulnerability (candidate genes) have been identified, each of them with a limited impact in terms of relative risk. Some of the more replicated findings have been in genes involved in myelinisation, neural and glial cell proliferation and glutamate transmission (e.g. neuregulin 8p21-22, DISC 1 1q42, dysbindin 6p22, KI 6q25-27 and COMT 22q11), and there is also some support for overlap in vulnerability with bipolar disorder. Of interest within the scope of this thesis, a proteomic approach showed that genes involved in energy metabolism and oxidative stress could differentiate nearly 90% of schizophrenic patients from controls.

The phenotype heterogeneity of schizophrenia complicates genetic research, and current DSM-IV sub-classification appears to be of limited use. Identification of endophenotypes (heritable state-independent markers associated with illness also found in non-affected family members at a higher rate than in the general population) may give clues regarding etiology and further genetic research. A number of neurological, neurophysiological, cognitive and other candidate endophenotypes have been proposed. Response to niacin that is investigated in this thesis has thus been proposed to serve as endophenotype candidate in schizophrenia.
Vulnerability factors

There is also support for a number of different vulnerability factors for schizophrenia that are hypothetically interacting with genetic risk factors. There is also support for a number of different vulnerability factors for schizophrenia that are hypothetically interacting with genetic risk factors. Among prenatal factors that can be mentioned are maternal prenatal nutritional deficiency and viral infections (in particular influenza) during the 1st or 2nd trimester. Further findings regard urban place of birth and winter birth. Obstetric complications are known to increase the risk for schizophrenia, and there is support for a co-variation between obstetric complications and reduced electrodermal activity. Low premorbid IQ and other premorbid cognitive signs are reported as risk factors but may also be part of the schizophrenia syndrome proper. An array of different factors during childhood and adolescence contribute to schizophrenia risk: central nervous system (CNS) infection, family history of migration, and cannabis abuse may be mentioned. Several of these are understandable based on the stress-vulnerability model of schizophrenia originating from Zubin and Spring 1977.

The transmitter theory

The transmitter hypothesis of schizophrenia postulates a disturbance in the regulation of brain neurotransmitters. The focus has been on dopamine since 1958 when the Swedish Nobel laureate Arvid Carlsson identified the substance as a neurotransmitter. Although there are many specific findings regarding dopamine transmission, the most robust supports for the dopamine theory in schizophrenia are indirect clinical findings. The first regards the efficacy of dopamine 2 receptor (D2) blocking agents on psychotic symptoms, and the second concerns the ability of dopamine agonists like amphetamine to cause psychotic symptoms. Metabolites of dopamine, however, tend to be low in schizophrenia. The issue of dopamine regulation is complex but to give a simplified picture, it is generally thought that schizophrenia comprises over-activity in dopamine transmission. However, the core negative symptoms of schizophrenia hypothetically correspond more to a hypodopaminergic condition. In fact, this view is supported by findings of lower availability of tyrosine, the precursor in dopamine synthesis, in the disease. In addition to dopamine, research has gained support for disturbances in other brain receptor systems in schizophrenia such as serotonin receptors, alpha 7 nicotinic, muscarinic, gamma-aminobutyric (GABA) and glutamate receptors. The glutamate transmission on the N-methyl D-aspartate receptor (NMDA) is of great interest. The substance kynurenic acid is involved in glutamatergic and dopaminergic regulation in schizophrenia and interestingly it has also been reported to be under prostaglandin mediation.
The neurodevelopmental theory

The neurodevelopmental theory postulates that patients who will later develop schizophrenia have suffered from a subtle cerebral maldevelopment in utero or early life. The disturbance may occur in the forming, proliferation, migration or differentiation of neural cells and may thus be present in the premorbid state. The neurodevelopmental theory is supported by well-replicated findings of volumetric brain changes in schizophrenia as well as morphological or cytoarchitectural alterations in temporal and frontal structures, in thalamus, striatum and cerebellum. Some of the risk factors mentioned above such as obstetric complications and prenatal virus infections may support the theory. When Kraepelin first formulated his theory of dementia praecox, a neurodegenerative origin was proposed. However, an absence of markers for neurodegeneration like gliosis in post-mortem brains of patients with schizophrenia is reported in most studies. Since the early years of neuroimaging when ventricular enlargement was first reported, an early and more stable disturbance that was found in first episode patients was suggested. While morphometric changes as well as intellectual and neuromotor deficits seem to be premorbid in schizophrenia, there have been several magnetic resonance imaging (MRI) studies supporting progressive gray matter changes in the past decade.

Along with the different symptom modalities of schizophrenia, disturbed brain neurocircuitry, especially regarding prefrontal connectivity, has been discussed and emphasised in studies with positron emission tomography (PET), MRI and diffusion tensor imaging (DTI). Disturbed sensory gating or filter function may contribute to the shortcomings in everyday activities for many patients and is also reflected in pathological findings like disturbed pre pulse inhibition (PPI) and backward masking. Disturbances in mirror neuron functioning may contribute to specific negative symptoms. Numerous other findings such as aberrant brain stem evoked potential, mismatch negativity and event related potentials (P50 and P300-amplitudes) also fit in this model.

The phospholipid membrane theory:

schizophrenia as a systemic disease

Schizophrenia is usually conceived as a disorder within the brain. A century of schizophrenia research has, however, reported numerous findings of peripheral aberrations. DF Horrobin first suggested a prostaglandin etiology in schizophrenia and later formulated the phospholipid concept of schizophrenia. According to this hypothesis, the disturbance of CNS development originates in an aberration in CNS phospholipid membranes. Regarding the very high content of omega 3 and 6 fatty acids in the brain – in particular arachidonic (AA) and docosahexaenoic acid (DHA), which are major neural
cell membrane constituents - it is plausible that these substances have a role in mental functioning. During growth and maturation it is essential to have an adequate supply of lipid nutrients for the multiplication and differentiation of nerve cells during the genetically programmed development of the brain. AA is also a precursor for prostaglandins, thromboxanes, leukotrienes and anandamide. The disturbance in phospholipid membrane composition is not restricted to the central nervous system but hypothetically affects all plasma membranes in the body and may, for instance, be detected in erythrocyte membranes. Several studies have shown low levels of polyunsaturated fatty acids (PUFA) in plasma\textsuperscript{112, 113} and erythrocyte membranes of patients with schizophrenia,\textsuperscript{114-118} and also in unmedicated patients,\textsuperscript{119-122} but these findings have also been questioned.\textsuperscript{123, 124} Low PUFA levels are also reported in other tissues, such as cultured fibroblasts and post mortem brain tissue.\textsuperscript{125-127} Replicated results have been low erythrocyte levels of the PUFAs that constitute substrate for prostaglandin synthesis such as AA. Similar findings have also been reported in other psychiatric illnesses and are therefore apparently not specific to schizophrenia.\textsuperscript{128-130} Low levels of PUFA may be a target for diet interventions, and supplementation with particularly eicosapentaenoic acid (EPA) and DHA in schizophrenia has been encouraging.\textsuperscript{131-135} However, one double-blind study failed to determine an effect of PUFA supplementation,\textsuperscript{136} and in the latest Cochrane review it is stated that the results remain inconclusive.\textsuperscript{137} The outcome of PUFA treatment has generally been more favourable in other psychiatric diagnoses like affective disorder.\textsuperscript{138}

In addition to decreased PUFA membrane content in schizophrenia there are other findings supporting the phospholipid hypothesis. The phospholipid membrane may be subject to oxidative stress, cytokine interaction or other immunological aberrations in schizophrenia.\textsuperscript{139} Further, the activity of calcium independent phospholipase A2 (PLA2) enzyme is reported to be increased.\textsuperscript{140, 141} PLA2 catalyses the release of fatty acids from membrane phospholipids. Studies with \textsuperscript{31}P (phosphorus) magnetic resonance spectroscopy (MRS) also indicate disturbed phospholipid turnover in schizophrenia.\textsuperscript{142, 143} In addition, reactivity to niacin - a vitamin substance that stimulates a prostaglandin mediated flush reaction - is diminished in schizophrenia\textsuperscript{144} and has been linked to PLA2 activity.\textsuperscript{145} The niacin test in schizophrenia is discussed in more detail below. Studies on tyrosine transport and muscle morphology also support the view of schizophrenia as a systemic disorder involving the cell membranes.\textsuperscript{89, 146, 147}
Treatment

Schizophrenia care from a historical perspective

From a community mental care perspective, the history of schizophrenia in Western society has been a history of seclusion. For centuries, patients with severe mental disabilities were kept apart from the rest of society and spent their lives in asylums. During the 19th century the prison-like asylums slowly changed towards mental hospitals. The apartheid concept of psychiatric care remained more or less unchanged until the second half of the 20th century when different views evolved. This paradigm shift was no doubt an effect of better treatment options with the introduction of specific antipsychotic medication. For the first time patients now improved in a more predictable way by means of pharmacological treatment. As in most Western countries the number of inpatient beds in Sweden has decreased radically. Today most patients do have an independent living, but there is a huge demand for meaningful occupational activities. In many cases the intended integration is only nominal; isolation is still a large problem.

Rehabilitation

Psychiatric rehabilitation involves supportive social services and patient skill development, but also careful dosing of antipsychotics to avoid counterproductive side effects. Schizophrenia rehabilitation thus relies on early intervention, crisis prevention, family support, social skills training and coping strategies. Cognitive behaviour therapy (CBT) may improve the symptoms and is valuable in helping patients with everyday coping strategies. Stress reduction is important and psychosocial intervention may also involve case management and psychoeducative measures. An integrated treatment trial (OPUS) with two years of assertive community treatment (ACT), psychoeducational family intervention and social skills training was thus shown to reduce both positive and negative symptoms as well as comorbid drug abuse, and adherence and user satisfaction were increased. However, a recent follow-up of the OPUS trial failed to show sustained effects three years after the intensive program for first episode psychosis was discontinued, indicating that the need for supportive rehabilitation is permanent in many cases.

Antipsychotic medication

When the phenothiazine substance chlorpromazine first came into use, it was a major breakthrough for schizophrenia treatment. The antipsychotic effect could later be related to catecholamine receptor binding – particularly dopamine – in the brain. Since then, a variety of different antipsychotic
medication (neuroleptics) have emerged. The group is characterised by antipsychotic effect, sedative but not sleep inducing properties, prolactin increase and extrapyramidal side effects (EPS). Basically, antipsychotic medication reduces psychotic symptoms and prevents relapse. Ideally, an antipsychotic agent should have efficacy in treating all the core dimensions in schizophrenia. However, while antipsychotics are proven to be effective against positive symptoms they are much less valuable in treating the negative or cognitive symptoms.

Antipsychotics alter brain dopamine metabolism. There has long been an awareness concerning the NMDA receptor and glutamate transmission in schizophrenia; this has resulted in interesting research on a completely new pharmacological principle targeting metabotropic glutamate receptors in the brain. However, all compounds available today have a varying degree of binding and blocking of brain dopamine receptors. The intended antipsychotic effect is thought to be due to blocking of D2 in mesolimbic and mesocortical dopamine pathways, while prolactin release and EPS are mediated via blocking in the tuberoinfundibular and nigrostriatal pathways. The dosage regimen for antipsychotics like haloperidol has changed markedly over the years with considerably lower doses nowadays. The high doses used earlier were aimed at controlling positive symptoms in an in-patient setting and not necessarily at improving rehabilitation outcome. However, research with PET has demonstrated that the dosing of D2-blocking substances is quite sensitive, the therapeutic window is narrow and higher doses cause EPS without improving antipsychotic efficacy. In addition to D2 binding, most antipsychotic drugs also have affinity for other receptors like serotonin, histamine and muscarinic receptors.

In some patients, treatment with antipsychotics is not sufficient for controlling positive symptoms and additional substances like lithium, benzodiazepines or antiepileptic drugs, may be beneficial. Additional non-pharmacologic treatments include the use of electro convulsive therapy (ECT). The use of transcranial magnetic stimulation (TMS) over the temporoparietal cortex is also reported to reduce auditory hallucinations.

The second generation antipsychotics

Second generation antipsychotics (SGA) have been available for the past 15 years. Most of these compounds (e.g. clozapine, risperidone, paliperidone, olanzapine, quetiapine, ziprasidon, sertindole) have a higher relative affinity for serotonin and other receptors as compared to D2 receptors. The SGAs are frequently called “atypicals”, although they are a rather heterogeneous group of substances and in what way they are atypical is a matter of debate. In general, SGAs are still thought to have a lower propensity to cause EPS, although there are also substances in the first generation like thioridazine with a low risk for EPS. SGAs are often marketed claiming an
alleged better efficacy for the treatment of negative symptoms, but in terms of functional rehabilitation outcome this can be questioned. Many patients prefer SGAs and there are studies suggesting higher quality of life (QOL) with these drugs, although others question any advantage in efficacy, QOL or cost-effectiveness. Comparative studies like the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) as well as other studies indicate a marginally better efficacy for SGAs regarding adherence and relapse. Nevertheless, the proportion of patients rehabilitated to return to work and vocational activities has not increased with the use of SGAs.

The second generation drugs have lower propensity to cause EPS but instead have other limitations like weight gain and metabolic disturbances that are discussed below in more detail. The side effects of antipsychotics have always been a limiting factor in schizophrenia treatment, and compliance with prescribed medication is often reduced due to their occurrence. In several well executed studies, long-term adherence was remarkably low. Medication non-adherence involves a significantly higher risk for relapse, and a well-known clinical fact is that the relapse often involves a long and troublesome struggle to regain a former functional level. Consequently, measures to improve attitudes to medication and treatment adherence in schizophrenia are of major importance. Dosing should be low, and a personal case manager working with patient motivation and continuity may improve both adherence and outcome. The use of depot formulation also reduces the risk for relapse.

The metabolic horizon

Obesity, somatic morbidity and mortality in schizophrenia

While health and fitness in Western societies must be actively maintained, many patients with schizophrenia suffer from negative symptoms and lack the necessary tools for this effort. Thus, without proper social and occupational stimulation there is a risk over the long run for a sedentary indoor way of living. Even with adequate treatment, many patients exhibit a striking lack of both mental and physical energy that obstructs rehabilitation labours. Only a few studies have tried to measure daily activity in schizophrenia but they indicate low levels. In extreme cases the negative symptoms will eventually lead to a chronic deficit state with the patient apparently living on very low energy levels. This aspect of schizophrenia was actually noticed very early. Indeed, case studies in the beginning of the 20th century that measured energy metabolism in dementia praecox or schizophrenia found levels that were lower than expected.

Whether of psychiatric origin due to negative symptoms, or due to physiological or pharmacological factors, schizophrenia is often accompanied by
Obesity. Obesity is increasing globally and may produce a wide range of comorbidities like coronary heart disease, hypertension, non-insulin-dependent diabetes mellitus, osteoarthritis and sleep apnoea syndrome. Obesity is defined by the World Health Organisation (WHO) as a body mass index (BMI) of 30 kg/m² or above while BMI 25-30 kg/m² corresponds to overweight. Physical inactivity is probably a major determinant of the increasing BMI levels worldwide. For patients with schizophrenia, obesity also implies a second stigmatisation beyond that of having a serious mental disease.

Central (abdominal) obesity is associated with the metabolic syndrome, increases the risk for cardiovascular disease (CVD) and thus correlates with higher mortality. There is a high prevalence of metabolic syndrome in medicated patients with schizophrenia, and unfortunately, there is also evidence that diabetes, dyslipidemia and hypertension are underdiagnosed comorbid diseases in many patients. Untreated schizophrenia may also be associated with increased visceral fat, although this has been questioned in a Chinese material. It is noteworthy that disturbed glucose regulation in schizophrenia was reported long before antipsychotic treatment emerged, and it has also been confirmed in later studies on untreated patients. Considered together, these findings suggest that schizophrenia comprises an inborn metabolic dysfunction per se that is independent of medication, but that is of importance for health and mortality.

Life-style consequences of schizophrenia can thus be detrimental to bodily health. The diet is often of inferior quality compared with eating habits in the general population, and the prevalence of smoking is high. Smoking and other life-style factors together with the above mentioned metabolic aberrations in schizophrenia contribute to an increased risk for CVD. The relative mortality risk is thus significantly higher in schizophrenia than in the normal population and has in part been related to neuroleptic treatment. It is therefore vital to start interventions aimed at weight-management and health as early as possible in schizophrenia rehabilitation.

Antipsychotic medication, weight gain and diabetes

While rehabilitation efforts are aimed at counteracting this prevalent background risk of metabolic disturbances in schizophrenia, the side effects of antipsychotic medication have a large iatrogenic impact. Weight gain caused by medication varies among patients and is substance dependent. The SGA are generally thought to have more severe metabolic side effects, but weight gain and diabetes was early recognised with phenothiazine treatment. Most antipsychotics can thus cause weight gain that in some cases can be rapid and unacceptable. This creates a difficult clinical dilemma where good antipsychotic efficacy must be weighed against potential health risks in the long run. In conclusion, during any antipsychotic treatment it is essential to monitor body weight, blood pressure, fasting plasma glucose and lipid profile over time.
The etiology of antipsychotic induced weight gain is as complex as for obesity in general, and involves physiological, behavioural and environmental elements. It has been suggested that up to 6000 different genes may be implicated in the regulation of appetite, energy balance and weight control. Numerous hormones, catecholamine, neuropeptides, immunological agents and other substances are thus involved in this regulation. The action may be on regulation of appetite but also on energy expenditure. Insulin receptors have been found in the arcuate area of hypothalamus, implying that insulin signalling has a role in weight control by affecting food intake and energy turnover. Other peripherally secreted substances including cholecystokinin, adiponectin and leptin have satiety effects while the relatively newly discovered peptide ghrelin has appetite-increasing signalling. The nucleus arcuatus in the hypothalamus is one of the meeting points where important afferents and efferents involved in weight regulation converge. Nevertheless, the singular impact of many of these agents alone seems to be limited and body weight is controlled by a complex and finely calibrated organisation that evidently has a strong genetic foundation.

The influence of some antipsychotic agents may cause a profound dyscalibration of this weight controlling system. Leptin levels have been reported to increase after antipsychotic treatment probably secondary to weight gain, data on adiponectin and ghrelin are less consistent. The exact molecular basis for neuroleptic induced weight gain is hence not known, but binding to neurotransmitter receptors, particularly serotonin and histamine H1 receptors may contribute. Polymorphisms in the serotonin 5-HT2C genome have been linked to antipsychotic induced weight gain, and this finding has been replicated but also rejected, and remains controversial. Other candidate gene studies have revealed several findings across the genome, among them in the adrenergic receptor and leptin genes.

The association between antipsychotic medication and abnormalities in glucose regulation in schizophrenia has been extensively studied. Dysglycaemia and diabetes are thus at least twice as common in schizophrenia as in the general population, and the risk appears to be higher with SGA treatment. There is also evidence that antipsychotic induced glucose dysregulation is independent of obesity, and that SGA may exert direct pharmacological influence on insulin release from pancreatic beta cells.

To conclude, the focus of discussion concerning antipsychotic induced weight gain has been on the increased appetite and energy intake. This is also in accordance with clinical observations of many patients reporting immediate and sometimes dramatically changed dietary habits, in some cases of a rather bulimic quality, after start of medication. However, the other side of the energy equation i.e. expenditure has been of much less interest. The complex signalling system controlling body weight involves appetite and reward mechanisms but also regulation of energy expenditure. Thus, disturbances in energy expenditure may contribute to the influence of antipsychotic induced weight gain.
Energy expenditure

Basic concepts and the role of energy expenditure in weight gain

As evident from the foregoing chapter, the prevalence of obesity, diabetes and other metabolic disturbances is higher in schizophrenia than in the general population, thereby conveying a higher risk for CVD and mortality. Further, it is obvious that the issue of weight control and the impact of medication is complex, involving a great number of genetic, epigenetic and environmental factors. However, it is also true that the issue of weight control in man can be reduced to a simple equation that expresses the turnover from chemical energy in food to thermal and mechanical energy:

\[
\text{Energy intake} = \text{Basal metabolic rate (BMR)} + \text{energy for physical activity} + \text{thermal effect of food}
\]

Physical activity thus involves purposeful exercise but also nonexercise activity thermogenesis, referring to small changes in posture and movements that have been reported to have a role in weight control.\(^{209}\) The energy equation can be much more elaborated and also formulated in different ways such as: Energy intake = work + heat production + energy storage.\(^{210}\) However, for everyday use and including the terms that can be influenced by volition, further simplification into a basic energy balance equation results in:

\[
\text{Energy intake} = \text{Energy output (utilisation)}
\]

Thus, if the intake is higher than the energy output there will be a positive energy balance and weight will be gained. Theoretically, low overall energy expenditure may thus be one of the components underlying weight gain.

A major part of the energy output is the BMR which represents an energy turnover confined to intracellular processes and vital functions at rest. BMR maintains body temperature and metabolic homeostasis and is used for muscular activity restricted to cardiac, respiratory and gastrointestinal movements. BMR is the greatest determinant of overall energy turnover and accounts for 60-70% of the total energy expenditure (TEE).\(^{211}\) Based on this large contribution of the total energy output, it is reasonable to assume an important role for BMR in weight regulation. The metabolic rate has a relatively strong genetic contribution,\(^{212}\)\(^{213}\) and the variation among human beings may imply that some persons are more vulnerable for weight gain than others. Low resting metabolic rate has thus been coupled to obesity,\(^{214}\) and a prospective longitudinal study reported that low energy expenditure at rest could predispose to future overweight.\(^{215}\)
How to measure energy expenditure

The energy in food is stored in the C – H bonds in carbohydrates, proteins and lipids. This potential energy is liberated through oxidative pathways converting these bonds to carbon dioxide (CO₂) and H₂O. Energy turnover thus implies oxidation processes that will result in heat production (thermogenesis). Heat production (total heat loss from the body) can be measured with direct calorimetry (e.g. whole body calorimetry) but these procedures are resource craving and complicated. Indirect calorimetry does not determine heat production; instead, oxygen (O₂) consumption and CO₂ production are assessed, reflecting thermogenesis from the oxidation processes. Indirect calorimetry can be performed with respirometry or with the use of oxygen and hydrogen isotopes (double labelled water method). Indirect calorimetry with respirometry is founded on several assumptions reviewed by Ferrannini, e.g. that all O₂ is used to oxidise fuels and that the CO₂ produced in relation to O₂ varies with the oxidation of different substrates. This ratio, the respiratory quotient RQ=CO₂/O₂, is approximately 0.7 for fat, 0.8 for protein and 1.0 for carbohydrates. The unit for biological energy is 1 kJ, which is equivalent with 4.186 kcal.

In a state of wakefulness but complete rest, indirect calorimetry determines BMR. BMR must thus be measured in a fasting state without the influence of external environment, physical movements or effects of drugs. Because of the strict requirements for BMR assessment (e.g. measured in the fasting state, in the morning after a night’s sleep but without leaving the bed), the resting energy expenditure (REE) is more frequently used. REE – sometimes called resting metabolic rate (RMR) – is more vaguely defined and will be somewhat higher than BMR.

The role of anthropometry and body composition

REE is dependent on gender, age, hormonal status, nutritional status and several anthropometric factors that must be taken into consideration. Basic anthropometrics include height, body weight and BMI. There are several different equations for calculation of expected REE. The predictive equations developed by Schofield that are based on gender, age, body weight and height have been used by FAO/WHO/UNU for energy and protein requirements. However, an important anthropometric factor for REE is also the proportion of metabolically active tissue in the body. It is thus essential to assess body composition variables for an approximation of the share of the metabolically active fat free mass (FFM) versus the inactive fat mass (FM). The organ contribution to REE is very high for brain, heart, liver and kidneys. There are several methods for body composition measurement and the precision increases with the complexity of the methods. Two-compartment models assess FM and FFM while 3-compartment models also
obtain information on body water.\textsuperscript{223} High precision is achieved with a 4-compartment model combining underwater weighing + bioelectrical impedance analysis (BIA) + dual-energy X-ray absorptiometry, however, some of these methods are demanding for certain patient groups. A more practical combination of BIA and calliper measurements of skinfold thickness has proven to correlate well with the 4-compartment model.\textsuperscript{224}

Some modern studies have used body composition measurements in schizophrenia, but the aim has mainly been to evaluate changes (increase in body weight and FM) after antipsychotic medication.\textsuperscript{198, 225-228} After the studies in this thesis were carried out, some results have been published confirming higher percentage of body fat in patients with schizophrenia.\textsuperscript{176, 229} Considering the extensive interest in metabolic disturbances in schizophrenia and the quite easy procedure for measurement of body composition, surprisingly few studies had used this method. In a methodology study using the deuterium dilution technique as a reference method, BIA measures proved to be a better indicator of obesity than BMI in patients with schizophrenia.\textsuperscript{230}

Historical studies on basal metabolism in schizophrenia

When the present research project was underway I encountered historical case studies on lower BMR in patients with schizophrenia or dementia praecox. These findings from the first part of the 20th century appeared to have fallen into oblivion, as the publications were not searchable in common medical databases on internet then. The use of newer antipsychotics brought about a growing but somewhat startled research community dealing with the more and more obvious metabolic disturbances associated with SGAs. However, these historical BMR investigations appeared to be unknown as they were not cited. Some reviews on antipsychotics and weight gain even raised the important question about energy expenditure, but did not mention the reports from the pre-neuroleptic era.\textsuperscript{231-233} The historical studies had several methodological drawbacks; they were case report studies and did not involve control groups or statistical calculations. Measured values were compared with standard levels that were mostly not specified, and diagnosing was uncertain. Further, the case series also often included different kinds of psychiatric and neurological diseases. One study made statistical comparisons with an unselected normal material but there were no anthropometric characteristics and no descriptions of methods.\textsuperscript{234} Nevertheless, several of the early studies included quite large case series and the findings are intriguing, especially in that the patients were untreated. The majority of patients with dementia praecox or schizophrenia in these studies showed lower BMR than expected, often -10% or lower, and it was also noted that agitated patients exhibited lower recordings.\textsuperscript{174, 175, 235-238} The studies did not offer any mechanistic explanation for the lower BMR, although there was great interest in
thyroid function in psychiatric patients at that time. In 1932 R.G. Hoskins wrote:

“Schizophrenia is a condition characterized, among other physiological abnormalities, by a systemic downward displacement of the oxygen consumption rate. The data as reported offer no evidence whether the displacement is causative of, consequential to, concomitant with or integral in the psychosis proper. The report serves chiefly to define a problem for further research.”

Recent studies on energy expenditure in schizophrenia

The few studies of REE in schizophrenia in recent times have been fuelled by the metabolic changes seen after introduction of SGA agents. Therefore they have been executed as intra-individual comparisons before and after SGA treatment and lack comparison with healthy controls. The possible question regarding a lower REE related to the disease itself and not to the medication has not been asked. Most of these study results point towards a fairly unchanged REE despite considerable gain in weight after start of treatment with SGA. One case report based on three patients reported decreased RMR after clozapine treatment, but REE was measured during unsatisfactory conditions, non-fasting and just after a short period of sitting. Another study failed to detect differences in REE between patients on clozapine, olanzapine and risperidone. The question of different predictive equations for REE has also been addressed in a case series of eight clozapine treated patients. Further, Sharpe et al used the double labelled water method to estimate TEE and the part of the expenditure that is due to activity in eight patients with schizophrenia. The levels were lower than expected and the report argues for finding methods to counteract the sedentary habits of the patients rather than to restrict the diet in order to prevent obesity. A recent study found an association between REE and fasting insulin levels in patients with schizophrenia, an interesting finding regarding the role of insulin signalling in the brain for weight control. Likewise REE, there is a paucity of modern studies on energy expenditure during work in schizophrenia and no studies measuring physical capacity with regard to relevant body composition parameters (FFM).

Energy expenditure from a phospholipid membrane perspective

It is estimated that during basal metabolic conditions approximately 90% of the oxygen consumption in the body is mitochondrial, of which 80% is coupled to adenosine triphosphate (ATP) synthesis and 20% is uncoupled by proton leak. Further, while a large part (25-30%) of the ATP synthesis coupled oxygen consumption is used for protein synthesis, 19-28% is used by the ion pump Na⁺-K⁺-ATPase for the maintenance of electrochemical
gradients across the cell membrane. Smaller amounts are used by other ion channels like the Ca\(^{2+}\)-ATPase. In the brain, Na\(^{+}\)-K\(^{+}\)-ATPase is a highly energy consuming enzyme and 50-60% of brain oxygen consumption is estimated to be coupled to the ion pump.\(^{242}\) It has also been demonstrated that dopamine has a regulatory effect on brain Na\(^{+}\)-K\(^{+}\)-ATPase activity.\(^{243}\)

According to the phospholipid theory of schizophrenia,\(^{111}\) a disturbance of membrane fatty acid composition will affect the functioning of all integral proteins including ion channels like Na\(^{+}\)-K\(^{+}\)-ATPase. There is also support for reduced Na\(^{+}\)-K\(^{+}\)-ATPase activity in unmedicated patients with schizophrenia.\(^{244, 245}\) Furthermore, preclinical studies have demonstrated that rats fed with an omega 3 deficient diet not only have reduced amounts of long chain PUFA in the brain but also a 40% reduction of Na\(^{+}\)-K\(^{+}\)-ATPase activity in nerve terminals.\(^{246}\) Thus it appears that the phospholipid membrane structure is involved in energy homeostasis. Cellular membranes have accordingly been suggested as “pacemakers of metabolism” with BMR directly influenced by the fatty acid unsaturation ratio in the membrane structure.\(^{247}\)

The niacin test

Niacin and the skin flush reaction

Niacin induced skin flush is reported to be diminished in schizophrenia and this finding has been interpreted as a sign of deficient eicosanoid signalling.\(^{144}\) Niacin (nicotinic acid) is a water soluble substance that after oral intake is absorbed in the jejunum and eventually excreted by the kidneys. It belongs to the vitamin B group but some niacin can in fact also be synthesised in the body. A metabolic step in the pathway from tryptophan to niacin is kynurenine, further metabolised to kynurenic acid, which is reported to be involved in the pathophysiology of schizophrenia. Niacin may be further converted to the ubiquitous oxidation-reduction enzyme nicotinate adenine dinucleotide (NAD) that has a central role in physiological energy metabolism. Niacin is an important cholesterol and triglyceride lowering agent but its capacity to induce a vasodilatory skin flush affecting the upper parts of the body has somewhat restricted its medical use. The recent finding of specific G-couple niacin receptors\(^{248}\) has triggered the search for agonistic compounds that may be used in hyperlipidemia, hopefully without the flush side effect of niacin proper.

The skin flush reaction is thought to be mediated by prostaglandins (PG),\(^{249}\) although serotonin may also be involved.\(^{250}\) PGD2 in particular shows an increase after niacin supply but PGE2 may also be released.\(^{251}\) PGD2 is synthesised by prostaglandin synthases from precursor PUFA AA that first is split from the phospholipid membrane by PLA2. PGD2 acts on capillary endothelial cells causing dermal vasodilatation. The prostaglandin release takes place in the skin and recent studies support Langerhans cells as the source.\(^{252}\)
The niacin test in schizophrenia

Interestingly, the specific niacin G-coupled receptors have also been found in the brain, and one type has recently been reported to be dysregulated in schizophrenia but not in bipolar disorder. Future research in this area may elucidate the possible role of niacin in schizophrenia. During the 1960s and 1970s attempts were made to use the compound as a treatment alternative, but its use was controversial and suffered from a lack of controlled studies. A metaanalysis failed to show positive results for niacin treatment in schizophrenia and the present status of evidence is rather unsatisfactory. The Internet homepage www.schizophrenia.com keeps track of alternative treatments and ranks niacin in the lowest group, comprising substances judged to have no treatment effect on the disease. It was, however, noted early that patients with schizophrenia appeared to react with less vasodilatation than expected after niacin ingestion. David Horrobin formulated a prostaglandin hypothesis and later incorporated the deficient niacin flushing in the more general membrane hypothesis of schizophrenia originating from findings of lower membrane PUFA.

Since then a fairly large bulk of investigations has studied niacin sensitivity in schizophrenia, although with different methods. The vast majority of studies report diminishing in some aspect of flushing. This is with one exception true for the oral niacin test. A topical test was developed by Ward and co-workers, and reduced flushing after topically administered niacin is described in several studies, and also in unmedicated patients. Niacin hypo-sensitivity has also been associated with an increase in PLA2 activity. The topical test provides the possibility of studying dose-response associations. However, the issue of what concentration of methyl nicotinate to use and at what time point in order to detect differences is complex and results vary from study to study. It is important to find the best cut-off measures if the reduced niacin response is to be used as a vulnerability marker. Somewhat conflicting results were found in one study reporting absent flushing only in first episode patients and not in chronic patients. However, recent large studies confirm the use of the blunted niacin flush response as a strong endophenotype candidate in schizophrenia. An interesting study found a bimodal distribution of niacin induced flush in male schizophrenia patients regarding two different genotypes of the fatty acid-CoA ligase type 4 (FACL4) enzyme.

Despite several findings of disturbed niacin sensitivity in schizophrenia, there is a lack of studies on stability. This issue is also intriguing, as a subsiding of the flush side-effect is known from hyperlipidemia treatment in other populations. There are two studies on repeated measurement in subgroups of schizophrenia patients after antipsychotic treatment and PUFA supplementation, but there are no retest studies in patients without intervention.
Electrodermal activity

Whereas the niacin test studies changes in skin blood flow and temperature, electrodermal activity (EDA) refers to changes in skin conductance. The skin conductance level (SCL) is dependent on both the presecretory and the secretory activity of eccrine sweat glands. In contrast to the apocrine glands located in armpits and genital areas, the eccrine glands cover a large part of the body and are most dense on the palms and soles of the feet. The sudomotor activity of eccrine glands and hence EDA is under strict sympathetic control although the neurotransmitter that mediates sweat gland activity is acetylcholine. Acetylcholine release triggers cellular influx of $\text{Ca}^{2+}$ that stimulates $\text{Cl}^-$ and $\text{K}^+$ channels causing efflux of potassium, chloride and water and, in turn, stimulation of sweat duct Na$^+$-K$^+$-ATPase resulting in hypotonic sweat solution. Prostaglandins and nitric oxide also appear to have a role although the details of sweat gland physiology are not yet fully understood. EDA as a marker for psychological activity was known as early as the 19th century and began with the discovery that the skin is a better conductor of electricity in the presence of external stimuli. EDA was thus associated with attention, arousal and emotions. The tonic EDA refers to SCL and the occurrence of spontaneous non-specific fluctuations in conductance (NSF) and is generally attributed to alertness and arousal. Phasic EDA variations like skin conductance responses (SCR) are useful for the study of attention, information processing and stimulus significance. SCR thus refers to transient increases in SCL elicited by different kinds of identifiable stimuli. The electrodermal system is under the control of excitatory and inhibitory pathways with influences from cortical areas, hypothalamus, the limbic system, basal ganglia and the reticular formation in the brainstem. Typical EDA measures include SCL, NSF, SCR and the habituation of SCR to repeatedly presented stimuli.

Both tonic and phasic EDA abnormalities are reported in schizophrenia, and the EDA aberrations have been linked to other findings like prevalence of negative symptoms, volumetric brain changes and outcome. There are two main findings that are replicated in almost all studies on patients with schizophrenia. The first is the failure to elicit SCR to innocuous stimuli (non-responding). Pooled data from several studies revealed that on average 43% of patients were non-responders compared with 14% of controls. The second well replicated finding refers to a higher autonomic activity including higher SCL, more NSF and impaired habituation to repeated stimuli. A bimodal distribution has thus been suggested in schizophrenia, with both non-responders and hyper-responders. Tonic hyperarousal has also been related to psychotic state while non-responding has been proposed to be a vulnerability factor. This is somewhat in contrast to findings of hyperarousal in individuals with high genetic risk for schizophrenia. EDA measures appear to have fair stability over time in patients with schizophrenia, as reported by Schell and co-workers in their study over one year and their review of previous test-retest studies.
Background to the present studies

As indicated in the introduction, disability due to schizophrenia depends to a large extent on the negative symptoms. In states of remission from more disturbing positive symptomatology the negative symptoms can dominate the clinical picture and many patients appear to have low mental and physical energy. Although a number of case report series presenting lower energy BMR in schizophrenia were published early in the 20th century, no such studies have been performed in modern times and to my knowledge no study has included comparison with a matched healthy control group and considered the influence of body composition variables.

Therefore, the first rationale for measuring REE in schizophrenia is a need to answer the question as to whether REE is lower in schizophrenia, thereby constituting a physiological correlate to the negative symptoms and to the impression of low energy in the clinical picture.

The second rationale is the importance of assessing REE to further understand the weight gain and metabolic disturbances, with subsequent higher mortality, issues that are apparently not only related to pharmacotherapy.

Third, there is a theoretical basis for a reduced REE in the earlier findings of low PUFA in schizophrenia combined with other findings concerning the importance of membrane PUFA for Na+K+ATPase and energy homeostasis.

Considering the high mortality in CVD and the very extensive interest in metabolic disturbances in schizophrenia during the past decade, there is a surprising lack of modern data on physical capacity. Again, to my knowledge, no studies have performed an ergometric test with continuous respirometric measurements while also considering the influence of body composition variables like fat free mass in patients with schizophrenia as compared with controls. Hypothetically, the low BMR suggested in the mentioned historical studies may have an influence on physical capacity.

Niacin response and electrodermal activity have not been studied previously in the same patients with schizophrenia. Theoretically, there is a strong connection between PUFA as substrate for prostaglandin conversion and the aberrant niacin flushing in schizophrenia. The mechanisms underlying EDA, are complex but a contributing role of skin physiology that may involve prostaglandins cannot be ruled out. This motivates the study of a possible correlation between the two tests in patients in comparison with controls.
Although several studies have assessed the stability of EDA parameters over time, few investigations have addressed the question of retest stability for the niacin test. Moreover, the temporal stability of both tests in the same patients has not been studied before.

Aims of the study
The principle aim of the studies in the present thesis was to gain deeper understanding of the pathophysiological mechanisms underlying schizophrenia, with particular interest in systemic and peripheral manifestations of the disease. The more specific aims were:

1. To study REE and relevant body composition measures in patients with schizophrenia in comparison with matched healthy controls.

2. To study energy expenditure and physical capacity during a controlled ergometric test in male patients compared with controls.

3. To study both niacin response and EDA in the same patients with schizophrenia compared with healthy controls.

4. To assess the test-retest stability of the niacin response and EDA in patients with schizophrenia.

Hypotheses

1. REE is lower in patients with schizophrenia than in controls.

2. REE correlates with ratings for negative symptoms.

3. Male patients with schizophrenia have a lower physical capacity than healthy male controls.

4. There is a diminished niacin skin flush response in patients but not in controls.

5. There is an association between niacin and EDA-responding.

6. The niacin response is stable at repeated testing.
Methods

The studies were executed at the Department of Psychiatry, Uppsala University Hospital. Three patients were investigated in 1998 and the remaining patients and controls from October 1999 to January 2003. The studies were carried out using a group to group comparison experimental design.

Participants

Consecutive patients from hospital wards and from outpatient care were asked to participate. Patients aged 18-50 years with schizophrenia or schizophréniform disorder were included. Exclusion criteria were major somatic disease, psychiatric disorder other than schizophrenia, concomitant treatment with antidepressant, anticonvulsant, antidiabetic or anti-inflammatory medication. Thirty patients, 21 males and 9 females, and 17 controls, 12 males and 5 females, were recruited to the REE study (paper I). In the ergometric study (paper II) only male patients and controls were recruited.

The healthy control group was recruited through a newspaper advertisement and was matched for age and gender. The healthy control group underwent the same examinations as the patients. Present or former psychiatric problems or first-degree relatives with psychiatric disease excluded participation.

There were thus 30 patients participating in the REE study and 30 in the niacin study, although only 28 patients participated in both studies. One male patient was excluded from the REE study due to non-compliance with the REE protocol as he had been up walking all night before the registration, but he could participate in the niacin study the next day. One female showed a very slight increase in fasting blood glucose that precluded participating in the REE-study but that was judged not to be of relevance in the niacin-study. There were also two patients and one control who were included in the project but excluded after the investigations started. One male patient was found to have a prescription of metoprolol 25 mg for hypertension. Another male patient had somewhat elevated liver transaminases and turned out to have sporadic alcohol abuse. One male control developed hypotension and panic during the niacin test, showed somewhat elevated psychiatric ratings and admitted that relatives had psychiatric disorders. Data regarding these three persons were not used for analysis.
The characteristics of the patients and controls participating in the REE-study are presented in table 1. There was no difference in gender composition between the groups. The differences in body weight and BMI between patients and controls were not statistically significant. Further details on different medications, etc., are described in the Materials and Methods section in paper I and for the niacin-EDA study in the Methods section in paper III.

In the ergometric study (paper II) 10 male patients who previously had participated in the REE study and 10 male controls were recruited. The patient group did not significantly differ in any relevant way from the remaining 11 male patients who had also participated in the REE study. They thus exhibited the same characteristics (age, duration, chlorpromazine equivalents and PANSS-ratings), anthropometrics (weight, BMI, FFM, FM), and calorimetric parameters during rest (REE and RQ). The reason for restricting the sample to males was the finding of gender differences in the REE study and the lack of power to perform gender analysis in a small sample. Ten healthy

*Neuroleptic medication is expressed as equivalents of chlorpromazine per day for the treated patients (n = 19). PANSS = Positive and Negative Syndrome Scale. Values are means (SD).

<table>
<thead>
<tr>
<th></th>
<th>Patients with schizophrenia</th>
<th>Controls</th>
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<tbody>
<tr>
<td>Gender (male/female)</td>
<td>21/9</td>
<td>12/5</td>
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<td>Age (years)</td>
<td>33.0 (8.7)</td>
<td>32.3 (7.9)</td>
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<td>23.7 (2.9)</td>
<td>0.16</td>
</tr>
<tr>
<td>Body surface (m²)</td>
<td>1.96 (0.21)</td>
<td>1.89 (0.2)</td>
<td>0.27</td>
</tr>
<tr>
<td>Blood glucose (mmol/l)</td>
<td>5.0 (0.5)</td>
<td>4.8 (0.5)</td>
<td>0.32</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>4.8 (0.9)</td>
<td>4.8 (0.9)</td>
<td>0.92</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.3 (0.9)</td>
<td>1.1 (0.6)</td>
<td>0.28</td>
</tr>
<tr>
<td>Triiodothyronine (nmol/l)</td>
<td>2.0 (0.3)</td>
<td>2.1 (0.4)</td>
<td>0.30</td>
</tr>
<tr>
<td>Thyroxine (pmol/l)</td>
<td>15.2 (2.9)</td>
<td>14.0 (1.9)</td>
<td>0.16</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>9.1 (8.7)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Neuroleptic medication (mg/day)*</td>
<td>342 (157)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PANSS total score</td>
<td>73.7 (17.1)</td>
<td>32.6 (1.6)</td>
<td>-</td>
</tr>
<tr>
<td>PANSS positive subscore</td>
<td>16.0 (4.4)</td>
<td>7.8 (0.8)</td>
<td>-</td>
</tr>
<tr>
<td>PANSS negative subscore</td>
<td>21.2 (6.2)</td>
<td>7.5 (0.8)</td>
<td>-</td>
</tr>
<tr>
<td>General Assessment of Function</td>
<td>33.9 (10.0)</td>
<td>86.9 (3.5)</td>
<td>-</td>
</tr>
</tbody>
</table>
controls matched for age were included in the comparison group. Details on participants in the ergometric study are described in the Methods section in paper II.

In the niacin-EDA retest study (paper IV) 23 patients agreed to repeat investigations after three months and seven patients were lost to follow-up. One data set for EDA was lost to analysis due to technical problems. The remaining six patients were dropouts for different reasons; one found the niacin flush reaction disagreeable, one perceived the neutral tone-stimuli in the EDA-paradigm as unpleasant, and the rest did not complete the tests due to lack of motivation or worsening of their psychotic state.

**Procedures**

Information, informed consent, interviews, physical examinations, and laboratory blood tests were performed in advance, in general 2-3 days before the physiological measurements. These were carried out with determination of body composition and REE day 1 (paper I) and EDA and niacin response on day 2 (paper III). After three months, niacin and EDA tests were performed again (paper IV). At a separate occasion (1-3 months after REE in most cases) the participants were examined with an extensive neurocognitive test battery (neurocognitive data are not presented in this thesis). The REE-findings motivated calorimetry during exercise, which was performed at a later occasion (paper II).

**Psychiatric ratings**

All patients and controls were interviewed regarding psychiatric and somatic disease. Ratings were performed with the Positive and Negative Syndrome Scale (PANSS), a modified version of the Extrapyrdamidal Symptom Rating Scale (ESRS) (data not presented here), the Global Assessment of Function scale (GAF), and a modified Strauss-Carpenter scale for social function (data not presented here). New ratings were performed after three months in the niacin-EDA retest study (paper IV) and also in connection with ergometry (paper II).

**Body composition**

Body composition parameters were assessed with bioelectrical impedance analysis (BIA) using a multi-frequency bio-resistance analyser that provided data on total body water (TBW), intracellular water (ICW) and extracellular water (ECW). A prediction of expected TBW was also made from anthropometric measurements. For the calculations of FFM, FM, body fat (BF) and water in fat free mass (WFFM) a three compartment model was used.
involving BIA combined with calliper measurements of the biceps, triceps, subscapular and suprailiac skinfolds. Details regarding apparatus and electrode placement are found in the Material and Methods section of papers I and II.

Resting energy expenditure

The REE method was rigorous and close to BMR requirements. All participants were thus fasting overnight and the measurement was performed in the morning with a minimum of muscular activity from the time of awakening in bed until the investigation. The participants were allowed to get dressed and were then directly transported to the laboratory. REE was measured with indirect calorimetry using a ventilated system with a dilution face mask connected to a Sensormedics respirometer for measurement of oxygen consumption and carbon dioxide production. REE was first calculated as kJ/kg body weight. The predictive equations provided by FAO/WHO/UNU, taking into account age, gender, weight and height, were then used for all participants to calculate an expected value. This predicted value was compared with the measured REE and the difference was expressed as ΔREE and as a percentage of reduction from expected value. Details regarding apparatuses, calibration, calculations of energy expenditure and respiratory quotient are found in Materials and Methods section in Paper I.

Physical capacity and energy expenditure during exercise

The measurement of physical capacity using an ergometric test was performed at a later occasion in a subset of 10 male patients from the REE study and 10 healthy male controls. The participants were fasting overnight and the measurement of body composition, energy expenditure during exercise, respiratory quotient and physical capacity were performed in the morning. The procedures for BIA analyses and indirect calorimetry were the same as described above. After body composition assessment the participants started a submaximal exercise test on an electronic cycle ergometer with simultaneous calorimetric registration. The initial workload was 50 W and the load was increased by 25 W when a steady state condition with low variability in heart rate (HR) was attained. Ratings of perceived exertion according to the Borg scale were performed and a submaximal exercise level decided with a HR of approximately 125-130 and Borg scale ratings of 13-15. A prediction of the maximal oxygen uptake (VO₂max) as a measure of physical capacity was made. Further details on procedure are found in the Methods section in paper II.
Niacin response and electrodermal activity
These assessments were carried out starting at about 10.00 a.m. the day after the calorimetric investigation of REE. The niacin test comprised a pharmacological intervention that could hypothetically also have impact on EDA. Therefore EDA was measured first. Assessment of EDA was performed about 3.5 h after food intake in a non-task, long stimulus interval paradigm. Auditory stimulation with orienting tones (85 dB, 1000 Hz) was presented through headphones at fixed intervals. Skin conductance level (SCL) was registered with electrodes affixed on the index and middle fingers of the left hand. Skin conductance response (SCR) was defined as an increase in SCL of 0.05 μS or more after a tone stimulus. EDA non-responding was defined as an absence of SCR to any of the first 2 tones. Further details on apparatuses, software, test conditions, definition and scoring of responses are found in the Methods section in paper III.

Immediately after EDA assessment an oral niacin stimulation test was performed with 200 mg of nicotinic acid dissolved in 100 ml of water. Skin surface temperature was continuously measured on the earlobes and recordings were performed at predefined fixed time points. A flush response
was defined as a rise in skin temperature of 2.0°C or more. Details on apparatus, administration and test conditions are found in the Methods section in paper III.

Procedures for the niacin test and EDA assessment at retest were the same as described above (paper IV).

Statistical analysis
The statistical softwares used were Statistica 6.0 – 8.0, and SPSS 12.0, 15.0.

Table 2. Statistics used in papers I – IV.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Statistical method</th>
</tr>
</thead>
<tbody>
<tr>
<td>I  REE</td>
<td>Two-tailed Students $t$-test, $\chi^2$</td>
</tr>
<tr>
<td></td>
<td>One-way ANOVA</td>
</tr>
<tr>
<td></td>
<td>Pearson’s correlation</td>
</tr>
<tr>
<td></td>
<td>Bonferroni correction</td>
</tr>
<tr>
<td>II ERGO</td>
<td>Two-tailed Students $t$-test, $\chi^2$</td>
</tr>
<tr>
<td></td>
<td>Mann-Whitney U-test</td>
</tr>
<tr>
<td></td>
<td>Pearson’s correlation</td>
</tr>
<tr>
<td>III Niacin EDA</td>
<td>Two-tailed Students $t$-test, $\chi^2$</td>
</tr>
<tr>
<td></td>
<td>Mann-Whitney U-test</td>
</tr>
<tr>
<td></td>
<td>Pearson’s correlation</td>
</tr>
<tr>
<td></td>
<td>Spearmans rank correlation</td>
</tr>
<tr>
<td></td>
<td>Phi ($\Phi$) coefficient</td>
</tr>
<tr>
<td>IV Niacin EDA re-test</td>
<td>Two-tailed Students $t$-test, $\chi^2$</td>
</tr>
<tr>
<td></td>
<td>Wilcoxon matched pairs test</td>
</tr>
<tr>
<td></td>
<td>Pearson’s correlation</td>
</tr>
<tr>
<td></td>
<td>Spearmans rank correlation</td>
</tr>
<tr>
<td></td>
<td>Phi ($\Phi$) coefficient</td>
</tr>
</tbody>
</table>

Ethics
All studies were performed according to the principles of the Helsinki Declaration and were approved by the Uppsala University Ethics Committee. The participants received full explanation of the nature of the study in the form of oral and written information and gave their written consent before participation in the study.
Results

Differences in resting energy expenditure and body composition between patients with schizophrenia and healthy controls (paper I)

The REE findings are depicted in table 3. The measured REE parameter (raw data) is of less interest since the groups were not matched regarding anthropometric data. The simplest outcome measure commonly used for REE, kJ/kg, was lower in the patients.

Table 3. Resting energy expenditure (REE).

<table>
<thead>
<tr>
<th>Patients with schizophrenia (n = 30)</th>
<th>Healthy controls (n = 17)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measured REE (kJ/day)</td>
<td>6720 (997)</td>
<td>6917 (1046)</td>
</tr>
<tr>
<td>REE/kg (kJ/kg/day)</td>
<td>85.3 (10.8)</td>
<td>94.4 (7.8)</td>
</tr>
<tr>
<td>Predicted REE (kJ/day)</td>
<td>7390 (1103)</td>
<td>7140 (1048)</td>
</tr>
<tr>
<td>ΔREE* (kJ/day)</td>
<td>-670.2 (728.7)</td>
<td>-223.8 (274.3)</td>
</tr>
<tr>
<td>REE % of predicted level</td>
<td>91.5 (9.8)</td>
<td>96.9 (3.6)</td>
</tr>
<tr>
<td>Respiratory Quotient (RQ)</td>
<td>0.81 (0.07)</td>
<td>0.80 (0.05)</td>
</tr>
</tbody>
</table>

*ΔREE is the difference between the observed metabolic rate and the predicted level for each individual according to the age-, gender- and anthropometry-related equations provided by the FAO/WHO/UNU. Values are means (SD).

The patients exhibited a significantly lower measured REE compared with the expected level according to the FAO/WHO/UNU equations that also corrected for other anthropometric data. The measured REE in the control group did not differ from the expected level according to the FAO/WHO/UNU equations. The relation between measured REE and the predicted level was the main outcome measure in the study and can be expressed either as the difference termed ΔREE, or the percent of expected value. ΔREE was thus lower in patients with schizophrenia than in the controls and this was also the case for REE expressed as percent of the expected
value (table 3). Fourteen of the 30 patients showed more than a 10% reduction from expected value compared with only one control (p=0.004).

Figure 2. Calculated difference in kJ/d between measured resting energy expenditure and the corresponding expected level for each subject according to the FAO/WHO/UNU anthropometry-related predictive equations.

Data on ΔREE for patients with schizophrenia and healthy controls arranged in increasing values.

Figure 2 shows the ΔREE values for all participants. A reasonable expected outcome would be that ΔREE for the participants would be within ± 400 kJ/d. This was the case for all but two controls while the majority of the patients had values outside these limits. In figure 2, N stands for non-medicated patient. Of the 11 non-medicated patients, five showed recordings below -10% of the expected value. There were no differences in ΔREE between medicated and unmedicated patients. It is evident that there was a considerably higher variation in the patient group and also a difference regarding gender. Of the patients, only females exhibited positive ΔREE values. All male patients showed lower than expected values and the eleven lowest ΔREE values were all found in males. The mean ΔREE was -944.3 kJ/d in males and -30.3 kJ/d in females, a highly significant difference. Figure 3 depicts ΔREE for the male and female participants in the two groups.
Figure 3. Gender differences.

Correlation analysis could not establish an association between any REE variable and PANSS scores.

Table 4 shows the results for the body composition measurements. Data on BIA was lost for analysis in two patients due to technical problems. The difference in body weight between the samples (table 1) was caused by significantly higher FM. The finding of similar FFM in both groups is of important for the interpretation of the REE results. The percentages of WFFM and ICW were lower in the patients compared with the controls. Body water in litres compared with predicted TBW according to Watson was also lower in the patients. While the non-medicated patients showed lower WFFM, differences in ICW, FFM, FM or BF were not significant compared with the controls. Detailed results for REE and body composition are found in paper I.
# Table 4. Body composition measurements.

<table>
<thead>
<tr>
<th></th>
<th>Patients with schizophrenia <em>(n = 28)</em></th>
<th>Healthy controls <em>(n=17)</em></th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total body water (TBW) (l)</td>
<td>39.6 (8.2)</td>
<td>41.2 (9.4)</td>
<td>0.53</td>
</tr>
<tr>
<td>ΔTBW* (l)</td>
<td>-5.1 (4.1)</td>
<td>-1.9 (3.2)</td>
<td>0.009</td>
</tr>
<tr>
<td>Water in fat free mass (%)</td>
<td>69.4 (2.6)</td>
<td>71.5 (2.2)</td>
<td>0.008</td>
</tr>
<tr>
<td>Intracellular water (%)</td>
<td>56.4 (3.1)</td>
<td>58.8 (3.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Extracellular water (%)</td>
<td>43.6 (3.1)</td>
<td>41.2 (3.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>56.6 (10.6)</td>
<td>57.1 (12.1)</td>
<td>0.89</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>23.1 (9.7)</td>
<td>16.6 (6.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>28.5 (8.6)</td>
<td>22.4 (9.1)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*ΔTBW is the difference between measured and predicted TBW according to the Watson formula. Values are means (SD).*

## Physical capacity, respiratory quotient and energy expenditure during exercise in male patients with schizophrenia compared with healthy controls (paper II)

In the ergometric study the patients with schizophrenia had higher mean body weight and BMI (see paper II) although the differences were not statistically significant. The patients had higher FM but almost identical mean FFM as the controls.

In the exercise test, the patients exhibited significantly lower physical capacity than the controls (table 5). This is evident already from lower workloads at submaximal work level when HR by definition was similar. The calculated VO$_{2\text{max}}$ was consequently lower in the patients. The lower VO$_{2\text{max}}$ remained after correction for weight and FFM (table 5).

On the fixed workloads of 50 W, 75 W and 100 W, the measured energy expenditure did not differ between the groups. However, RQ, as a measure of the substrate oxidation during exercise, was significantly higher at workloads of 75 W and 100 W (figure 4). One patient discontinued the exercise test already at 50 W load and three patients at 75 W. At 75 W there was thus data for nine patients and at 100 W data for six patients available (figure 4).
Table 5. Measurements at submaximal exercise level and calculation of maximal oxygen uptake capacity.

<table>
<thead>
<tr>
<th></th>
<th>Patients with schizophrenia n=10</th>
<th>Control subjects n=10</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submaximal work load (W)</td>
<td>87.5 (17.7)</td>
<td>130.0 (25.8)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Submaximal heart rate</td>
<td>132 (13)</td>
<td>126 (7)</td>
<td>0.18</td>
</tr>
<tr>
<td>Borg scale I, Median (range)</td>
<td>15 (13-17)</td>
<td>13 (11-17)</td>
<td>0.064c</td>
</tr>
<tr>
<td>Borg scale II, Median (range)</td>
<td>14.5 (9-17)</td>
<td>13 (12-16)</td>
<td>0.14c</td>
</tr>
<tr>
<td>VO$_{2\text{submax}}^d$ (ml/min)</td>
<td>1471 (219)</td>
<td>1852 (293)</td>
<td>0.004</td>
</tr>
<tr>
<td>VO$_{2\text{submax}}^d$ (ml/kg/min)</td>
<td>16.3 (4.4)</td>
<td>23.4 (5.9)</td>
<td>0.006</td>
</tr>
<tr>
<td>VO$_{2\text{submax}}^d$ (ml/kgFFM/min)</td>
<td>21.5 (4.7)</td>
<td>28.1 (5.7)</td>
<td>0.011</td>
</tr>
<tr>
<td>Predicted VO$_{2\text{max}}^e$ (ml/min)</td>
<td>2400 (467)</td>
<td>3620 (913)</td>
<td>0.002</td>
</tr>
<tr>
<td>Predicted VO$_{2\text{max}}^e$ (ml/kg/min)</td>
<td>26.5 (7.7)</td>
<td>45.8 (16.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>Predicted VO$_{2\text{max}}^e$ (ml/kgFFM/min)</td>
<td>37.2 (8.8)</td>
<td>55.9 (16.4)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

FFM = Fat free mass. $^a$ Borg scale ratings of central/respiratory exertion, $^b$ Borg scale ratings of peripheral/muscular exertion, $^c$ Mann Whitney U-test, $^d$ Measured by indirect calorimetry, $^e$ Prediction according to Astrand-Ryhming. Values are means (SD).

Figure 4. Mean respiratory quotient (RQ) during progressively raised workload.
Niacin skin-flush response and electrodermal activity in patients with schizophrenia and healthy controls (paper III)

The patients with schizophrenia had a slower flush development after niacin ingestion compared with the controls. The time to reach maximal skin temperature ($t_{\text{max}}$) was thus significantly longer in the patient group compared with the controls (table 6).

There were more EDA non-responders in the patient group than in the control group (table 6). The number of SCRs and the ratio of SCR and NSF were lower in the patients. SCL, NSF and trials to habituation did not differ between the groups.

Table 6. Niacin sensitivity and electrodermal activity.

<table>
<thead>
<tr>
<th></th>
<th>Patients with schizophrenia ($n = 30$)</th>
<th>Healthy controls ($n = 17$)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niacin flush response (yes/no)</td>
<td>25 / 5</td>
<td>14/3</td>
<td>0.93$	ext{a}$</td>
</tr>
<tr>
<td>Increase in temperature ($^\circ$C)</td>
<td>3.14 (1.31)</td>
<td>3.26 (1.00)</td>
<td>0.74</td>
</tr>
<tr>
<td>Time interval to 2.0 $^\circ$C (min)</td>
<td>16.56 (12.31)$^\text{b}$</td>
<td>10.86 (4.9)$^\text{c}$</td>
<td>0.11</td>
</tr>
<tr>
<td>Time interval to $t_{\text{max}}$ (min)</td>
<td>26.41 (14.59)$^\text{d}$</td>
<td>14.12 (6.83)</td>
<td>0.002</td>
</tr>
<tr>
<td>EDA response (yes/no)</td>
<td>16 / 14</td>
<td>14/3</td>
<td>0.047$^\text{a}$</td>
</tr>
<tr>
<td>Skin conductance level (μS)</td>
<td>3.55 (3.25)</td>
<td>2.50 (1.10)</td>
<td>0.21</td>
</tr>
<tr>
<td>Skin conductance responses</td>
<td>2.03 (2.79)</td>
<td>5.12 (4.50)</td>
<td>0.011$^\text{f}$</td>
</tr>
<tr>
<td>Non-specific fluctuations</td>
<td>1.49 (2.63)</td>
<td>2.31 (3.71)</td>
<td>0.38</td>
</tr>
<tr>
<td>SCR/NSF ratio</td>
<td>2.41 (1.52)$^\text{f}$</td>
<td>4.35 (2.72)$^\text{d}$</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Flush is defined as a rise in skin temperature of more than 2.0 $^\circ$C. Values are means (SD). $^\text{a}$χ², $^\text{b}$ $n = 25$, 5 patients did not reach 2.0 $^\circ$C, $^\text{c}$ $n = 14$, 3 controls did not reach 2.0 $^\circ$C, $^\text{d}$ $n = 29$, 1 patient did not show any increase in temperature, $^\text{e}$Mann-Whitney U test, $^\text{f}$ $n = 16$, $^\text{g}$ $n = 14$.

Figure 5 depicts the proportion of participants who reached $t_{\text{max}}$ at every time point. For example, at 10 minutes 3.3% of the patients had reached $t_{\text{max}}$ compared with 41.2% of the controls. The proportion of patients who had reached $t_{\text{max}}$ was thus significantly lower at every time point between 8 and 45 minutes. The number of patients who were niacin non-responders did not differ from controls. Neither the time elapsed to flush ($> 2.0^\circ$ C temperature increase), nor the magnitude of temperature increase differed between the groups (table 6).
For the two dichotomous response variables niacin response and EDA response, a significant correlation was found in the patients but not in the controls. Thus niacin non-response implied EDA non-response in the patient group. Further details on the results and their relation to clinical characteristics are found in paper III.

Figure 5. Percent of the participants who had reached $t_{\text{max}}$ at each time point after niacin ingestion.

Test-retest stability of the oral niacin test and electrodermal activity in patients with schizophrenia (paper IV)

Twenty-three patients underwent a retest of niacin response and EDA three months after the first investigation. There were greater numbers of both niacin and EDA non-responders at retest compared with baseline but these differences were not significant. The time elapsed to flush and to $t_{\text{max}}$ was similar at retest compared with baseline. However, there was no significant correlation for any niacin variable between the two test occasions (table 7). Regarding EDA; response, SCL and SCR correlated between test and retest (table 7).
Table 7. Niacin skin flush and electrodermal activity. Test and retest data.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Retest</th>
<th>Correlation Coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Niacin test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niacin response (yes/no)</td>
<td>19/4</td>
<td>15/8</td>
<td>0.39^a</td>
<td>0.06</td>
</tr>
<tr>
<td>Time to flush (min)</td>
<td>16.53 (12.75)</td>
<td>17.87 (8.95)</td>
<td>-0.34^b</td>
<td>0.25</td>
</tr>
<tr>
<td>Time to max temp (min)</td>
<td>24.68 (14.28)</td>
<td>26.13 (11.43)</td>
<td>-0.1^b</td>
<td>0.75</td>
</tr>
<tr>
<td>Temperature increase (°C)</td>
<td>3.42 (1.09)</td>
<td>3.30 (0.98)</td>
<td>-0.27^b</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>Electrodermal Activity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDA response (yes/no)</td>
<td>10/13</td>
<td>6/17</td>
<td>0.48^a</td>
<td>0.02</td>
</tr>
<tr>
<td>SCL (μS)</td>
<td>3.64 (3.61)</td>
<td>3.18 (1.66)</td>
<td>0.76^b</td>
<td>0.0001</td>
</tr>
<tr>
<td>SCR (no)</td>
<td>1.70 (2.55)</td>
<td>1.17 (2.01)</td>
<td>0.49^c</td>
<td>0.02</td>
</tr>
<tr>
<td>NSF/min</td>
<td>1.47 (2.85)</td>
<td>0.67 (1.39)</td>
<td>0.14^b</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Time to flush and increase in temperature refers to niacin responders, n=19 at baseline and n=15 at retest. All other parameters n=23. Values are means (SD).

SCL=skin conductance level, SCR=skin conductance responses, NSF=non-specific fluctuations. ^aPhi (Φ) coefficient for binominal data, ^bPearson’s correlation coefficient, ^cSpearman rank correlation.

A change in response patterns was seen in several participants for both of the tests, with conversion from response at baseline to non-response at retest and also vice versa (see paper IV). Despite this variation, the association in response patterns between the two tests that was previously found (paper III) was replicated; niacin non-response implied EDA non-response also at re-test.
Discussion

The present investigations were performed in order to achieve further understanding of the pathophysiological mechanisms underlying schizophrenia with a particular interest in peripheral and systemic manifestations with relevance also for the increased risk of obesity and metabolic complications seen in the disease.

Methodological considerations

Sample

The project involved studies on at least four days, and the participation was demanding even without considering the trying character of indirect calorimetry. The ambition was to recruit both antipsychotic naïve patients and patients with chronic schizophrenia, but a large number declined participation. From a certain time point in the project a log was created for all patients who were asked about participation, but several patients declined participation prior to that. A comparison of these patients versus the included patients is therefore not possible, which may restrict generalisation from the data obtained. A limitation is thus that a flow chart of participant recruitment in accordance with the CONSORT guidelines cannot be carried out. The patients included in the present project were in the ages 20-50 years, with a duration span of 0.2 to 28 years and with paranoid, disorganised, undifferentiated and schizophreniform subtypes of schizophrenia represented.

A major limitation of the studies is the low sample sizes that restrict possibilities for subgroup analysis. There was an equal gender distribution in the patient and the control group, although there were more males than females in both groups. The male dominance in clinical studies of patients with schizophrenia is a well-known dilemma, and gender differences in the disease will be discussed further below. An unexpected problem in the REE study (paper I) was the very high variation in REE due to gender that was found in the patient group, complicating further subgroup analysis regarding symptomatology and medication.

Although the differences found in the ergometric study (paper II) were pronounced, the sample size was low and limited to male patients of whom 90% were treated with antipsychotics, facts that may restrict generalisation
to the overall population of patients with schizophrenia. In the test-retest study of niacin response and EDA (paper IV) there was an almost 25% dropout rate from the original sample and considering the quite high rate of transformations in response patterns for both of the tests a larger sample would have been preferable.

The matching principle (papers I, II & III) was age and gender. This was most likely sufficient in the niacin response and EDA study (paper III) but for the calorimetric studies a strict matching regarding also anthropometric parameters would also have been desirable (papers I & II). Also matching for BMI could thus improve control of variation due to FM and FFM, but this would require a large number of potential controls to choose from. Matching for age, gender and additional anthropometric parameters is difficult to achieve in practise and was not possible within the scope of the present project.

Methods

The studies of REE and physical capacity (papers I & II) also determined body composition parameters relevant for the interpretation of calorimetric data and the assessment of metabolic status on the whole. BIA is generally considered to give fairly accurate estimates of fluid fractions and body fat but has its shortcomings in different populations like severely overweight or abnormally hydrated patients. Since 40-60% of the total body fat is subcutaneously distributed, the fat fraction can be assessed with calliper measurements. One drawback with this technique is the risk for inter-observer error. However, calliper measurement reliability is considerably improved when performed by the same experienced investigator, as was the case in the present studies. The combination of BIA and the calliper method that was used, has also been proven to correlate well with the complex gold standard method of body composition measurement.

The method of indirect calorimetry for measurement of energy expenditure is widely used and accepted. However, the measurement of REE implies several possible pitfalls. The first challenge lies in assisting participants to achieve a state of complete rest in an unfamiliar laboratory environment. All kinds of muscular activity increases the REE and this is also true for psychic factors that cause excitement and that will increase sympathetic activity. The quest for attaining a state of rest is considerably aggravated when investigating psychotic patients of whom several are first-episode, paranoid and unmedicated. There is a large risk for bias resulting from anxiety and fidgeting, and such bias may hypothetically produce higher REE recordings in the patient group in accordance with the higher ratings on PANSS for positive symptoms, anxiety and tension. There is thus reason to believe that the REE values found were not recorded in a true resting state in some of the patients. A methodological drawback to the design was therefore the lack of struc-
tured ratings of arousal, tension and small muscular movements during the recordings. Some patients later said that they had been worried during the experiment and not at all in a resting state and, in contrast to the controls, some were observed to be fidgety and actually not compliant with the protocol regarding rest. This form of bias produces falsely higher values and although not measured, these observations of higher arousal can be considered to support the validity of the lower ΔREE levels actually found in the patients. In the realm of speculation, the energy expenditure in a true state of rest may have been even lower.

Apart from bias from tension and movements, there are many other known sources of variation when measuring REE. Some of these are dealt with using the predictive equations, namely gender, age and basic anthropometrics in the form of body weight and height. Body composition parameters and particularly FFM are of major importance but not included in the FAO/WHO/UNU equations. A strength of the present study is the thorough measurement of body composition that permits the exclusion of possible differences in FFM as an explanation for the lower ΔREE in the patients. Nutritional factors influence REE, and reductions are seen in semi-starvation that, to some extent, have been attributed to a decrease in FFM. According to BMI and body composition results, there were no signs of undernourishment in the participants of the present studies. To control for effects of recent food intake, the BMR protocol was followed with fasting for a minimum of 10 hours before REE measurement. Data from diet registration for an overall estimation of food habits would have been valuable. Furthermore, hormonal status may influence REE. Thyroid hormones were measured and did not differ between patients and controls. Sex hormones may increase REE, and androgens more so than oestrogens, thus constituting one of the causes of the gender difference that is controlled for in the predictive equations. Testosterone substitution has been demonstrated to raise energy expenditure in hypopituitary men, but the impact of physiological variation in androgens is less clear. Androgens were, however, not measured in the present study, which is a drawback. Regarding female sex hormones the effects on REE are probably of less significance, although treatment with oral contraceptives may cause minor variation in REE. In the REE study (paper I) one female patient used contraceptives as compared with two of the controls. Furthermore, the accuracy of indirect calorimetry can be improved if urine nitrogen excretion as a measure of protein oxidation can be obtained and included in the calculations of energy turnover. This correction was not performed in the present study. However, unless there is a pronounced protein overload in the diet, the impact of protein is negligible constituting an error of < 2% in energy expenditure.

Another potential pitfall concerns the use of normative equations for expected energy expenditure, as all such equations involve approximations. The Schofield equations used for energy requirements by FAO/WHO/UNU
were based on a large sample of over 7000 individuals but – as is the case with other predictive equations – they have often been criticised for over- or under-estimating BMR in different populations. However, according to a review by Speakman and Selman, there is no evidence that modern Western populations have a reduced BMR relative to these predictive equations. Still, as BMR appears to be influenced by several other factors including environmental determinants like living in different climate zones, the construction of a universally valid equation is probably not possible. This potential bias, though hazardous in studies designed to determine nutrient requirements, is to some extent managed in a control group design. The FAO/WHO/UNU equations used for data on ΔREE and REE % in paper I were applied for both groups, and the result for the patients were compared with the results in a matched control group. However, there was also a significant difference when measured raw values for the patients were compared with the FAO/WHO/UNU prediction in the patients. In the control group the measured raw value was non-significantly lower than predicted which may support the hypothesis that to some degree the Schofield equations also overestimated REE in the participants in this study. Sharpe et al critically evaluated different predictive equations for REE, including the Schofield equations used in the present project, in a sample of eight clozapine treated patients. As all equations overestimated REE, the authors raise the question of whether the predicted level recommended for daily energy intake should be reduced for patients taking clozapine. However, that study design did not include the comparison with a healthy control group that would have facilitated interpretation of a potential systemic error. Furthermore, effects of schizophrenia rather than treatment could not be assessed, although the authors note that research is needed to sort out the possible effects of disease, drug therapy and lifestyle on REE.

Regarding the ergometric test (paper II), a superior method for measuring physical capacity would have been the execution of a maximal work test. In a maximal test, the ongoing calorimetric registration also provides continuous information on energy expenditure and RQ on work levels also above the anaerobic threshold. However, a maximal test is demanding, and even in studies dealing only with healthy control subjects there may be motivational issues. Several of the patients in the present study found the ergometric task strenuous and struggled to reach even the defined submaximal level. When dealing with a sample of subjects not used to physical exercise, there are also ethical and medical concerns with a maximal work test. The submaximal test procedure is thus widely used, as well as the algorithms for prediction of VO2max. An assessment of everyday activity and exercise habits was not performed, which is a drawback. The activity level of patients with schizophrenia is reported to be low and, although not determined, was probably low also in the present sample as the ratings on PANSS negative subscale may indicate. The prediction of VO2max according to Aastrand-Ryhming has...
been widely used but is intended for submaximal work within aerobic metabolism. Therefore, the prediction should be interpreted with caution when RQ is already high at a submaximal level, indicating an approaching anaerobic threshold. This was the case in the patient group, and such hypothetical bias in the prediction of VO$_{2\text{max}}$ will result in false high values. Thus, the real difference in VO$_{2\text{max}}$ between the groups, if assessed with a maximal work test, may be even larger than the prediction demonstrated.

The present study of niacin and EDA-response (papers III & IV) used an objective measurement of the flush reaction, which is a strength compared with some of the previous oral niacin studies that have relied on a visual assessment of flush. The temperature was measured continually with fixed interval readings. A continuous recording may have been preferable but would most likely not change the outline or interpretation of data. There was also a standardised 4-h postprandial procedure as the flush reaction is known to be milder if ingestion is accompanied with food. The use of an oral method involves possible pharmacokinetic issues that were not controlled for. Niacin is absorbed in the jejunum and the absorption may be influenced by factors like nutritional status and peristaltic movements. A methodological difficulty concerns the choice of an adequate niacin dose. The 200-mg dose has been used in other studies, but lower doses have also been utilised. The response to transdermally applied niacin differs a great deal for different doses, and there appears to be an optimal dose window for separation of patients and controls, although this dose window differs somewhat in different studies. While some questions arise concerning the transdermal test, there are also obvious benefits. The possibility of obtaining a dose-response relationship is of value, and the very limited local flush reaction is most likely perceived as less troublesome by the participants. The reason for using the oral test in the present investigations was the fact that the topical test had not been developed when the study was planned.

For EDA a well-known stimulus paradigm with innocuous tone stimuli was used and the scoring of all the participants’ recordings was performed by the same investigator.

To conclude, there are several methodological issues in the study but there are also strengths. The rigorous method for REE with the aim of reducing bias from muscular activity is a clear advantage compared with other recent studies in schizophrenic patients. The use of thorough body composition assessment is another essential advantage. The assessments of REE and VO$_{2\text{max}}$ relative to the FFM therefore add to the validity of the findings in papers I and II and contribute to the originality of the work, since such investigations have not previously been performed in patients compared with controls. Further, the combination of the two peripheral markers niacin response and EDA is a novel approach. In every study, reliability issues were minimised by the fact that ratings were performed by the same investigator, and this was also true for scoring procedures and physiological measurements.
General discussion

The hypotheses and the findings

In accordance with the hypotheses, the studies in the thesis found significantly lower REE than predicted in patients with schizophrenia compared with controls (hypothesis 1); lower physical capacity in male patients compared with controls (hypothesis 3); reduced response to oral niacin in the patients (hypothesis 4), and an association between niacin and EDA non-responding in the patients (hypothesis 5). The corresponding null hypotheses are thus rejected.

ΔREE was significantly lower in the whole patient group (hypothesis 1) but a major part of the variance was explained by gender and only the male patients actually exhibited a lower level (figure 3). This was an unexpected finding. However, the gender effect found influenced the design of the subsequent ergometric study, and the research hypothesis was thus limited to male patients compared with male controls (hypothesis 3). Regarding niacin, the diminished sensitivity found (hypothesis 4) did not involve the magnitude of the flushing, which was similar in both groups; it involved the temporal aspect of flushing with a postponed reaction in the patients.

A negative correlation between energy expenditure and PANSS negative symptoms was hypothesised (hypothesis 2) but could not be established, and the null hypothesis could not be rejected. This is somewhat surprising as negative symptoms are often found clinically in patients with an apparent low-energy way of life. A type II error due to limitations in sample size and confounding factors like gender cannot be entirely ruled out, but there was a lack of correlation between any of the REE parameters and any negative symptom. The present study thus failed to demonstrate a physiological correlate to the negative component in the clinical picture.

The study also failed to prove test-retest stability for the niacin test in patients with schizophrenia (hypothesis 6). On the group level, high homology between test and retest was found in data values for temporal measures in the niacin test (table 7), but correlation analysis revealed low test-retest stability. Regarding the niacin response criterion, an intraindividual variation was seen, with some patients transforming from response to non-response. Nevertheless, the p-value for test-retest correlation in niacin flush response was 0.06, representing a tendency. There is thus risk for a type II error and larger studies are warranted to clarify this issue.

The lower WFFM and ICW in patients with schizophrenia are interesting and hypothesis-generating findings but they did not originate from a specific research hypothesis. These results together with the lower sensitivity for both niacin and electrodermal activation found in the patients are interpreted in the context of systemic aberrations of schizophrenia. Regarding REE, this is an entirely systemic phenomenon as it is derived from processes in every
cell of the body. In the present study, the displacement of REE from the expected value was, however, limited to male patients. The explanation for this gender difference is presently unknown, but the issue is discussed below regarding gender differences in the clinical picture of schizophrenia. The displacement of REE, the drastic increase in RQ during low workload, and the low oxygen uptake capacity found in the male patients may be expressions of a disturbed homeostatic regulation of metabolism of relevance for the understanding of obesity, metabolic complications and increased CVD mortality that are seen in schizophrenia.

Possible explanations for the findings

The low resting energy turnover in the patients may be interpreted as a systemic manifestation particularly in the male form of schizophrenia. Although larger studies are warranted to control for effects of medication and environmental factors, this notion is supported by the historical studies that found a 10% or larger reduction of BMR in many patients with schizophrenia who were not treated with antipsychotic medication. The present study could exclude a difference in the metabolically active FFM as a possible cause of lower metabolism. For the moment there are no data supporting a mechanistic explanation for the finding, but several speculations can be proposed.

The first line of evidence supporting a systemic aberration in schizophrenia that may affect REE comes from the phospholipid hypothesis. According to the membrane hypothesis of schizophrenia, the precise composition of fatty acids in the plasma membrane is of vital importance for the function of membrane-bound proteins like neurotransmitter receptors and ion channels. The long-chain PUFA belonging to the omega-3 and -6 series have a molecular configuration characterised by the several double bonds that form bends or loops in the carbon chain. Saturated fatty acids have straight inflexible chains. Differences in chain structure will affect membrane function when incorporated in phospholipids, and the more complex structure of long-chain PUFA is thus important for membrane fluidity. If AA and DHA are low, the membrane is composed to a greater degree of saturated or mono-unsaturated fatty acids, creating a more rigid structure. This will cause a different chemical microenvironment of particular importance for membrane function in synaptic areas and hypothetically also change the function of integral proteins. There is thus compelling preclinical evidence for down-regulation of Na+K+ATPase activity after a PUFA deficient diet that decreases the unsaturation index of neural membranes.246 Interpreted in a phospholipid context, the finding of low REE is also in accordance with the hypothesis of biological membranes as regulators of energy expenditure.247 Clinically, there is also support for the value of long-chain PUFA substitution for symptom improvement in schizophrenia.131-135
A second line of evidence concerns mitochondrial function in schizophrenia. The brain is totally dependent on aerobic metabolism and the main energy generating pathway (>95%) is oxidative phosphorylation in the mitochondrial respiratory chain. The content of mitochondria is therefore very high in the brain, and brain tissue will be most vulnerable to a reduction of aerobic metabolism. Mitochondrial dysfunction and reduction of the ATP level may convey several negative effects including inhibition of ion pumps, increased oxidative stress, lipid peroxidation and apoptosis. A mitochondria hypothesis of schizophrenia is therefore attractive for the explanation of the pathology and symptomatology of the disease. Possible mitochondrial disturbances are also interesting for the interpretation of the present findings of both low energy and low water fractions (paper I) as well as low aerobic capacity (paper II) in the patients. Several studies have revealed reduced activity of cytochrome C oxidase activity in the respiratory chain in brain tissue from patients with schizophrenia. Signs of mitochondria deficiency have also been reported and have been detected in lymphocytes from patients with schizophrenia, and lymphocytes have thus been suggested to serve as a peripheral model of altered energy metabolism in schizophrenia. A very interesting issue for energy expenditure during rest and work are the functions of mitochondrial uncoupling proteins (UCPs) and peroxisome proliferator activated receptors (PPARs) that have central roles in cellular energy metabolism and are regulated by fatty acids. In an extensive proteomic and genomic investigation of brain matter from patients with schizophrenia, Prabakaran et al reported, among several other relevant findings, that oxidative phosphorylation and ATP synthesis were significantly downregulated, and also concluded that genes related to energy metabolism or oxidative stress could differentiate 90% of patients from controls.

Muscle tissue has high mitochondria content. Flyckt et al reported differences in muscle morphology in patients with schizophrenia compared with controls. This report is interesting also from a functional aspect in relation to the findings of the present study (papers I & II). FFM, the compartment that is indicative of muscle mass, did not differ between patients and controls, but REE was still lower than expected in the patients.

Related to the mitochondria hypothesis is the third line of evidence coming from studies with $^{31}$P MRS. The method has the advantage of reflecting phospholipid fractions and phosphorus containing metabolites in the living brain. Although the findings are not altogether unequivocal, there is evidence for disturbances in the brain turnover of high-energy substances in schizophrenia. Several studies have also found reduced levels of ATP in frontal lobes, temporal lobes and basal ganglia.

Since hypofrontality in schizophrenia was first reported, several MRI and PET studies have been performed. Although the literature is not entirely consistent, findings of reduced regional or global brain metabolism in
schizophrenia have been reported, further motivating the study of overall metabolism in schizophrenia.\textsuperscript{308-310}

The finding of lower body water fractions in schizophrenia (paper I) was not expected, but is interesting both from a clinical point of view and in comparison with other research results. As percentage of total body water is dependent on the fat mass, the lower WFFM is the more solid result. The fraction of intracellular water was also low in the patients. The result is strengthened by a similar finding of low intracellular and total body fluid in schizophrenia.\textsuperscript{311} The finding of low WFFM offers no insight into the mechanism, but from a phospholipid membrane point of view, lower ICW is intriguing in terms of water transport over the membrane. The at least 13 different aquaporin subtypes has several functions besides water permeation. Their role in neural function is not yet fully understood but it has been proposed that they are of importance for brain energy metabolism.\textsuperscript{312}

The low WFFM is also interesting regarding the occurrence of polydipsia, a well known but poorly understood phenomenon. The prevalence of mild polydipsia is possibly higher than recognised clinically.\textsuperscript{313} More uncommon although not rare, is polydipsic water intoxication in patients with schizophrenia, leading to deranged electrolyte balance and in severe cases development of a fatal condition.\textsuperscript{313} Hypothetically, the urge to drink water may have its origin in a dysregulation of body fluid homeostasis. To further assess this issue, studies of water fractions in identified polydipsic patients during periods with and without polydipsic behaviour are needed. Another rather speculative question concerns what role such dryness may have in the volumetric findings of reductions in brain matter found in several studies.\textsuperscript{101}

A lower physical capacity in male patients with schizophrenia was evident from a lower workload and lower calculated VO\textsubscript{2max} in the submaximal test, but also from the increasing RQ (paper II). In fact, in the patients the rapid rise in RQ even at moderate load, indicates quick transition to anaerobic metabolism when load is increased above submaximal levels. This restricts oxygen uptake and therefore the patients were hypothetically close to their maximal oxygen uptake already at a submaximal level. This, in turn, implies that the already low calculated VO\textsubscript{2max} in the patients may actually be an overestimation. All patients had exhibited low energy expenditure in rest in the former study (paper I) and supposedly they thus had to elevate their energy turnover relatively more than the controls to meet the energy demands for cycling on the fixed workloads. Though not significantly different due to the small sample size, the patients in the ergometric study had a higher body weight and BMI than the controls. As discussed in paper II, VO\textsubscript{2max} is corrected for body weight and the weight of FFM. The major influence of weight on VO\textsubscript{2max} is thus considered to be explained by FFM.\textsuperscript{314} Regarding RQ, several studies have reported similar levels in obese and non-obese healthy subjects during submaximal work.\textsuperscript{315, 316} However, a high RQ indicates carbohydrate combustion rather than oxidation of fat and there is
support for a correlation between a high 24-h RQ and the risk for weight gain in a healthy population. Many patients with schizophrenia report carbohydrate craving.

Another interesting issue is the potential influence of activity and training on $VO_{2\text{max}}$. It is well known that exercise implies both short-term and long-term improvements in physical capacity. Regarding the low results in the patient group, the question concerning the amount exercise that can improve the oxygen uptake capacity therefore becomes vital. Then again, the answer is dependent on what populations are studied, and the issue is complex. Kahn et al performed an extensive review and meta-analysis of different community interventions and behaviour changes and their efficacy with respect to physical capacity in the general American population. Aerobic capacity thus increased by median of 8.4% for different educational and health behaviour programs and by median of 6.3% for individually adapted programs. According to a recent study, elite athletes exhibited an approximately 15% higher $VO_{2\text{max}}$ compared with untrained controls. In the present study (paper II), the predicted $VO_{2\text{max}}$ expressed as ml/min was on average 51% higher in the controls compared with the patients, 73% higher when expressed as ml/kg/min, and 50% higher in the controls when FFM was included in the ratio. These differences are large even when hypothesising that the patient group had very sedentary habits. The risk for vicious circles is obvious, and it is plausible that the pronounced increase in RQ and the very low $VO_{2\text{max}}$ can limit the ability to engage in everyday activities. The question as to whether the reduction in physical capacity that was seen is a cause or a consequence of a low activity level cannot be answered by the present study. However, the pronounced findings in the ergometric study, together with the low REE and the low fluid levels (paper I), are hypothetically interpreted as expressions of a homeostatic dysregulation of metabolism in patients with schizophrenia.

Patients with schizophrenia exhibited reduced reactivity to niacin compared with controls (paper III). This is in accordance with the phospholipid theory of schizophrenia postulating an aberration in the supply of PUFA or in the conversion to prostaglandins necessary for the vasodilatation reaction. The niacin test thus showed a delay in the temperature increase after oral intake of niacin in the patients, but failed to detect any difference in temperature increase compared with the controls. Postponed flush in schizophrenia has also been reported with the topical test. The failure to replicate differences between patients and controls regarding flush/non-flush and magnitude of increase in skin temperature may have several possible explanations. One is the dose of nicotinic acid used. There is an obvious dose-response relationship regarding the vasodilatation in the topical test and the 200 mg oral dose employed in the present studies may thus be too high.

The results in the EDA assessments (paper III) are in agreement with earlier studies. More patients with schizophrenia exhibited EDA non-
response compared with controls and the patients also had less SCRs. As a group the patients were thus hypo-responding, although there were some patients who exhibited large numbers of NSFs and more trials to habituation; however, such hyper-responding individuals were also found in the control group. A significant relationship for EDA and the niacin test regarding the dichotomous parameter response/nonresponse was found only in the patient group, and this association was also replicated at retest (paper IV). This is in accordance with our hypothesis, and also with a possible role for PUFA and phospholipid membrane status for EDA. Again, as there are no data on PUFA, this reasoning is speculative. However, there is research supporting a role for prostaglandins in sweat gland activity, and the autonomous regulation of vasodilatation and eccrine perspiration have points in common. Hypothetically, there may be a peripheral aberration in skin physiology in schizophrenia that is of importance for both reactions. A disturbance in membrane lipid chemistry can hypothetically also interfere with the higher autonomous control of phasic EDA.

Specificity of the findings

An important question is whether the lower REE compared with the expected level (paper I) is specific to schizophrenia and not found in other psychiatric diseases. The above mentioned historical studies of BMR often recruited case series with mixed psychiatric diagnoses as well as neurological or infectious disorders with manifestations. Although a low BMR was most prevalent in cases with schizophrenia, some of these studies also described lower values in cases with affective disorders, while BMR was reported to be normal in most patients with neurosis. One contemporary study demonstrated higher RMR in 10 seasonally depressed patients compared with controls, while another found low RMR in 11 depressed patients. The latter study did not involve a control group and none of these studies applied measurements of body composition. A recent study reported lower REE in 15 patients with bipolar disorder than in controls. This report describes comparisons with four predictive equations but used a simplified REE method with a portable calorimeter and did not assess body composition. Nevertheless, if the results are valid, it appears that low REE is another finding that bridges the Kraepelinian diagnosis gap between schizophrenic and affective psychosis. Several other similarities between the disorders have been reported and there are also phospholipid aberrations found both in schizophrenia and affective disorder. To sort out potential diagnosis-specific changes in REE, studies are warranted that include both patients with schizophrenia and patients with bipolar disorder in comparison with controls.

Modern REE-data on samples with other psychiatric diagnoses are scarce. A recent study with indirect calorimetry and euglycemic insulin clamp failed to detect any difference in energy expenditure in violent offenders with anti-
social personality disorder compared to controls, although several other metabolic aberrations were found.\textsuperscript{324} Higher BMR was found in boys with attention deficit hyperactivity disorder.\textsuperscript{325} As reviewed by de Zwaan et al 2002, REE is reported to be lower in underweight patients with anorexia nervosa, although the difference disappears in most studies when corrected for FFM.\textsuperscript{326}

Regarding the finding of lower WFFM (paper I) it is presently unknown if this is a perturbation specific to schizophrenia, or also existing in other psychiatric conditions.

Low physical capacity is a rather non-specific finding and, as discussed above, some physiological variation due to activity levels is certain and reductions of VO\textsubscript{2max} are also seen in several somatic conditions. Ergometric studies on psychiatric patients in modern times are scarce, and there is a lack of studies taking anthropometric factors like body composition into consideration. The few existing reports are older or deal with mixed groups of mental illness rather than schizophrenia.\textsuperscript{327-329}

The majority of studies with niacin have been performed in schizophrenia. A slight niacin hyposensitivity is reported in dyslexia,\textsuperscript{330} but with one exception,\textsuperscript{331} studies with both oral and transdermal niacin tests have failed to demonstrate reduced sensitivity in affective disorder\textsuperscript{259, 332} and the sub-sensitivity is proposed to be specific to schizophrenia.\textsuperscript{333} A familial aggregation has also been demonstrated with intermediary sub-sensitivity in family members compared with probands and controls.\textsuperscript{67, 68} These results give fairly strong support for the absent niacin response as an endophenotype marker in schizophrenia.

EDA hyporesponsivity has also been found in depression.\textsuperscript{334} In fact, electrodermal abnormalities are also found in a variety of neurological diseases like CNS lesions, peripheral neuropathies, Parkinson’s disease and multiple sclerosis.\textsuperscript{271} Thus, EDA abnormalities are apparently not disease specific, but they are of great interest for different aspects of schizophrenia like outcome and symptomatology. Aberrations like hypo-responding have also proven to be quite stable findings in schizophrenia. The association between response patterns for the niacin test and EDA found in patients with schizophrenia (papers III & IV) has not been investigated in any other disease.

The role of antipsychotic medication

Antipsychotic medication may influence energy expenditure in several ways. Some preparations prolong the sleep and the time spent in bed and thus the average daily muscular activity and TEE are decreased. Some antipsychotics also have sedative or relaxing properties that will reduce TEE.

Chlorpromazine and other antipsychotics are lipophilic agents that can accumulate in plasma membranes and hypothetically modify membrane structure and permeability. In an early review, Palatini thus summarised
preclinical findings regarding direct inhibitory effects of phenothiazine antipsychotics on Na+K+ATPase activity, and hypothesised that such inhibition will depress energy-producing reactions. Further, mitochondrial cytochrome complex I activity was found to be reduced in rat brain after haloperidol and fluphenazine administration and has also been demonstrated to be inhibited by different antipsychotic medications in a dose dependent way in brain specimens from humans, and also by haloperidol in mononuclear blood cells from patients with schizophrenia. These findings are intriguing, but for the moment, preclinical as well as clinical studies in patients with schizophrenia do not support any major influence of antipsychotics on energy expenditure.

Based on observations in eight patients, Sharpe et al argued that REE is lower than predicted in persons taking antipsychotic medication, but the study lacked comparisons with controls and unmedicated patients, and it is therefore difficult to separate pharmacological influences from disease effects. In healthy subjects, REE corrected for FFM did not change after two weeks of treatment with olanzapine or risperidone in spite of weight gain. Similar findings of unchanged REE despite weight gain, are reported in patients with schizophrenia after the start of SGA therapy. The only contrasting finding is a case report with three patients that describes decreased REE after clozapine treatment. However, the report has major methodological drawbacks; the patients were not fasting and were just sitting quietly for 15 min, there were also many concomitant medications including other antipsychotics, and no body composition assessments were performed. At the moment there is thus more evidence for the notion that antipsychotic medication has a limited influence on REE. Our present data (paper I), also pointing towards lower ΔREE in the unmedicated first episode patients suggests a disease-effect, but larger studies including antipsychotic naïve patients, medicated patients and matched controls are warranted.

Regarding the influence of antipsychotics on fluid fractions, Kivircik et al studied body composition in a sample of patients after clozapine treatment and reported decrease in total body fluid compared with pre-treatment. However, this finding may be explained by the fact that there was also an increase in fat mass in their patients. In the present study (paper I), a post hoc analysis also showed lower levels of %WFFM in the untreated patients.

The role of antipsychotic treatment regarding the niacin sensitivity in schizophrenia has only been investigated to a limited extent, but some studies with the topical test have confirmed blunted skin flushing also in untreated patients. To our knowledge there are no studies devoted to antipsychotic naïve patients using the oral test. Antipsychotics, at least substances with strong anticholinergic mechanisms, may be hypothesised to influence the absorption of oral niacin. The untreated patients in the present study (paper III) had somewhat longer delay to maximal temperature increase after niacin ingestion compared with the treated patients although the
difference was not significant. There were no differences in niacin outcome measures between treated or untreated patients.

With reservation for the small sample size, no clear effects of medication could be seen on EDA parameters in the present studies. Neuroleptic treatment may contribute to reduced tonic EDA, especially SCL, but minimally to phasic EDA, although a slightly smaller incidence of non-responding may be found in non-medicated patients.\textsuperscript{341}

### Influence of smoking

The prevalence of smoking has always been higher in schizophrenia than in other psychiatric conditions and it has previously been reported that 80 – 90\% of the patients are smokers.\textsuperscript{342} Smoking has decreased in Sweden and this decline has probably also included patients with schizophrenia. The figures found in the present studies are lower, with 43\% in the REE-study and 40\% in the niacin-EDA study. It is often said that smoking in schizophrenia represents an attempt to self-medicate symptoms. There is some support for beneficial effects of smoking on antipsychotic adverse effects, sensory gating disturbances (PPI and P50) and cognition. Nicotine thus modulates dopamine transmission in limbic and nigrostriatal structures and can also influence cortical glutamate transmission.\textsuperscript{343} Influences of nicotine in limbic reward-reinforcement systems are hence thought to counteract amotivational and anhedonic symptoms related to disease or pharmacotherapy. A hypothetical question is whether smoking could be explained as an attempt to increase the energy metabolism in schizophrenia. Smoking a pack of cigarettes increases the TEE by about 10\%,\textsuperscript{344} and both high- and low-nicotine cigarettes are also reported to increase REE.\textsuperscript{345} In the present study (paper I) there were no significant differences between smoking or non-smoking patients in any outcome variable.

In the ergometric study (paper II), 60\% of the patients were smokers compared to none of the controls. In this small sample of patients, there were no differences in VO\textsubscript{2max} (ml/min/kg) in the non-smoking patients compared with smokers. A Swedish study of 144 healthy men reported approximately 11\% higher VO\textsubscript{2max} (ml/min/kg) and 4\% lower RQ in non-smokers compared with smokers but no differences between non-smokers and users of smokeless tobacco.\textsuperscript{346} However, the literature is not consistent, and there are studies that failed to determine any relationship between smoking and oxygen uptake capacity.\textsuperscript{347}

Smoking appears to have slight influence on EDA,\textsuperscript{348} but is seldom discussed in studies of patients with schizophrenia. The absent niacin response is reported to be independent of nicotine use.\textsuperscript{333} In the present study (paper III), the patients who were smokers showed tendencies for less SCR and also faster niacin response when compared to the non-smoking patients, although the differences were not significant.
Gender differences
The results from paper I indicate that gender has a large influence on energy expenditure in schizophrenia. The differences may be explained by a different metabolic regulation in male and female patients. Gender differences regarding the clinical picture are well known. Females tend to fall ill somewhat later in life, they often exhibit less negative symptoms at onset, they have higher social function and better coping strategies and they may consequently have a better prognosis. Estrogens may have neuroprotective abilities in schizophrenia. The risk for first psychotic symptoms in females is thus higher when estrogen levels are low, e.g. postpartum or during menopause, and estrogens have also been suggested to have a therapeutic role in schizophrenia.

There was no clear variation due to gender in the niacin-EDA studies (papers III & IV). Regarding the topical niacin test, a weak decrease in flush response over age and lower flush response in males are reported in healthy controls, but are generally not mentioned in the literature on patients with schizophrenia. Correlation between obstetric complications and EDA hypo-responding was reported to be stronger in females than males. Wieselgren et al found that EDA hypo-responding was associated with poor outcome in males and hyper-responding with poor outcome in female patients with schizophrenia.

Clinical implications
The results from the REE study contribute to our understanding of the clinical picture and the rehabilitation difficulties often seen in patients with schizophrenia. Some patients have a very low activity level and the present study confirmed that the energy level at rest is lower than expected in male patients. It may thus be of clinical value to identify those patients who exhibit a large downward displacement and an obvious question is whether specific interventions or pharmacological therapy can be developed for this aspect of the disease. The finding also highlights an increased metabolic sensitivity, especially in male patients with schizophrenia. A plausible hypothesis is that low energy expenditure in patients with schizophrenia may contribute to an increase in FM in the long run. Antipsychotic treatment, especially some of the SGAs, may thus be a sufficient provocation to evoke weight gain and future metabolic complications in a physiologically vulnerable patient group.

More convenient methods for measurement of energy expenditure have emerged lately with portable calorimeters easy to use also in a clinical setting. Also BIA is a fairly uncomplicated method that would add clinically relevant information, e.g. data on FM and BF, for the evaluation of antipsychotic related weight gain.
The finding of low physical capacity in the ergometric study adds increased knowledge concerning the risk for cardiovascular disease in schizophrenia and emphasises the importance of physical exercise for this patient group. Physical activity has beneficial effects in reducing risks for diabetes, cardiovascular disease, ischemic stroke, osteoporosis and depression. Further, activity improves quality of life and may reduce psychotic symptoms. Clinical awareness of somatic concerns in schizophrenia has increased during the past decade and algorithms for screening of diabetes and hyperlipidemia have been developed. In many centres there are now programs for lifestyle interventions but such measures should be mainstreamed and included in general guidelines for the care of patients with psychotic diseases.

Episode markers are those measures that differentiate schizophrenic patients from normal subjects only as long as the episode persists. Vulnerability markers are those measures that differentiate schizophrenic patients from normal subjects before, during and after the episode and that are relatively permanent traits. EDA aberrations have been coupled to an array of clinical findings in schizophrenia and have been proposed as markers for vulnerability, psychotic episodes, as well as outcome. Also the topical niacin test has been found to indicate vulnerability in several studies but related to first-episode in another study. One important question regards the potential utility of a niacin test as a possible marker of PUFA deficiency in providing guidance regarding supplementation of omega-3 fatty acids. There is some support for this idea, although large-scale studies that simultaneously measure PUFA-levels and niacin response are yet to be performed. Both the oral and the topical tests are fairly easy to administer in routine clinical praxis, but the challenge lies in finding discriminating doses and interpreting possible habituation effects with repeated exposure. The stability of the niacin response must thus be further assessed.

Ethical considerations

The indirect calorimetric technique used may be quite demanding for patients with psychotic symptoms. The patients had to wear a dilution face-mask connected to a registration apparatus and also maintain a state of rest for about 1 hour in the REE study. It can be difficult to cope with these requirements for first-episode unmedicated patients who, sometimes also have persecutory delusions. It is noteworthy that most recent studies on psychotic patients that have used this technique have included small numbers of patients. The trying character of indirect calorimetry protocols for patients with mental illness and the difficulty to recruit participants to such studies is also discussed by Sharpe et al.
Taking this into consideration, the present study (paper I) included a relatively large sample of 30 patients of whom 11 were unmedicated and 10 of whom were in an acute first episode state. To optimise a trustful atmosphere we took pains to carefully inform the patients about the character of the investigation. There was also a psychiatrist or psychiatric nurse present during every registration. Even with these precautionary measures, two of the patients told me afterwards that they had frightful paranoid thoughts during the calorimetric registration. The risk for misinterpretation of even carefully given information is higher in acute paranoid states. This emphasises the need to be alert and sensitive during more complex research activities involving participation of patients with schizophrenia.

The oral niacin test was well tolerated by almost all of the participants. However, some of them nevertheless reported that the flush side effect was unpleasant. The use of transdermally applied niacin reduces the exposure and the flush to a minimal part of the body, which thus implies fewer ethical considerations. Regarding EDA, the non-task method used has no major ethical issues, yet the innocuous tones were perceived as threatening by one of the patients, once again highlighting the vulnerability of the patient group.

Future research

The finding of the REE-study is in accordance with several historical observations on low basal metabolism in schizophrenia. It is therefore interpreted as sign of a true biological aberration in patients with schizophrenia or possibly in a subgroup of patients with schizophrenia. Whether the finding represents a state or trait phenomenon remains unclear but the low intraindividual variation in REE in the general population should be kept in mind and supports a trait view. The only way to answer this question is to perform larger confirmatory studies during different stages of disease. Low REE may serve as another endophenotype marker useful for subgroup classification and further genetic research.

The present study does not contain data on PUFA levels which would have been preferable and this was actually intended originally. The question whether the lower REE than expected may be explained by aberrations in membrane fatty acid composition is intriguing. Studies assessing membrane PUFAs, water fractions and energetics in patients with schizophrenia have not been performed and are therefore warranted. PUFA deficiency is also widely used as an explanation model in several niacin studies. In spite of this, there are no major studies that have determined both fatty acid levels and niacin sensitivity. To sort out the effects of REE and the impact of antipsychotic medication on long-term weight gain, longitudinal prospective studies would be rewarding.
In schizophrenia, subtle aberrations in the brain cause functional disturbances like psychotic symptoms and social disability. There are, however, also a multitude of findings regarding disturbances outside the CNS indicating a systemic manifestation in the disease. In the present thesis different physiological variables were studied in patients with schizophrenia compared with healthy controls. The main results may be summarised as follows:

I  Patients with schizophrenia exhibited lower resting energy expenditure than controls. A gender difference was found with lowest values in the male patients. The finding was not explained by difference in body composition or medication.

II  Lower percentages of water in fat free mass and of intracellular water were found in the patients irrespectively of gender and antipsychotic medication.

III  Male patients had lower physical capacity and a faster rise in respiratory quotient during exercise compared with controls.

IV  Patients with schizophrenia had a delayed flush reaction after niacin ingestion and exhibited hypo-responding electrodermal activity.

V  There was an association between response patterns for niacin reactivity and electrodermal activity in the patients but not in the controls.

VI  Electrodermal variables exhibited reasonable stability at repeated testing but there was low test-retest stability for niacin measures. The association in response patterns was replicated at retest.
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This picture was made for a poster when I was doing basic med-school training in 1987. For some reason I included both a mitochondrion and a flying phospholipid membrane in the picture, matters that have a place in the discussion part of this thesis.
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