Neurophysiological correlates of the pathway to the early stages of psychosis

van Tricht, M.J.

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GENERAL INTRODUCTION
1.1 THE SCHIZOPHRENIA CONCEPT

Schizophrenia is a severe and chronic mental disorder characterized by a heterogeneous course and varying signs and symptoms in the vast majority of patients. Patients are classified to suffer from schizophrenia when they show two or more characteristics symptoms, including i) positive symptoms, i.e. hallucinations, delusions, and disorganized speech or behavior and ii) negative symptoms, e.g. loss of initiative, flattening of affect or social withdrawal (American Psychiatric Association, 2000). Additionally, although cognitive impairments are not yet required for a diagnosis, these impairments are commonly acknowledged as a core feature of schizophrenia (Elvevåg & Goldberg, 2000). The symptoms are accompanied by marked disturbances in social or occupational functioning. The prevalence of schizophrenia is estimated at 0.7%. Age at onset varies, but the first signs and symptoms usually manifest themselves in adolescence or early adulthood (Mueser & McGurk, 2004).

Despite interventions, including cognitive behavioral therapy, family therapy, and/or antipsychotic medication, the prognosis of schizophrenia remains variable and in around 50% of the patients poor. Estimates of increased relative risk of suicides vary from 1.9 to up to 10%, with the highest risk of suicide occurring soon after the first psychotic episode (Dutta, 2010). Moreover, schizophrenia is associated with a lower life expectancy compared to the general healthy population, due to amongst others high comorbid obesity and excessive smoking (Insel, 2010).

One of the currently dominant theoretic frameworks to explain the development of schizophrenia is the neurodevelopmental hypothesis. In short, this model states that the schizophrenia syndrome has its origin in disturbed development of the nervous system. Specifically, both early (i.e., abnormalities in pre- and perinatal periods) and late (e.g. abnormal synaptic pruning during adolescence) neurodevelopmental processes are thought to participate in the aetiology and pathophysiology of schizophrenia (Cannon et al., 2003; Owen et al., 2011). Environmental risk factors may include prenatal exposure to infections or fetal distress, depression of the mother during pregnancy and living in an urban environment. Furthermore, prospective and retrospective studies have shown that individual risk factors include meningitis, urban rearing, low IQ and substance abuse (e.g. cannabis).

1.2 PREDICTION OF PSYCHOSIS

1.2.1. Prodromal phase

The successful treatment of schizophrenia is still a major challenge in psychiatry (Ruhrmann et al., 2012). As it has been demonstrated that the duration of untreated psychosis may adversely effect the course of schizophrenia (Marshall, 2005) and early intervention methods, including integrated psychological intervention (e.g. cognitive behavioural therapy), may delay the onset of psychosis (Bechdolf et al., 2012; van der Gaag et al., 2012), researchers worldwide have aimed at identifying subjects at putative risk of psychosis, before the onset of a full-blown psychotic episode. During the past few decades, the focus of schizophrenia research has therefore shifted to the
prodromal phase, i.e. the period preceding the onset of the first florid psychotic episode, in which increasing symptomatic presentation as well as functional deterioration are observed (Nieman et al., 2007; Yung et al., 2003). The length of this phase, that occurs in approximately 75% of the cases, varies from a few months up to five years (Häfner & An der Heiden, 1997). In addition to early intervention purposes, investigating subjects in a putative prodromal phase may also aid in the identification of behavioral, cognitive, and neurobiological risk markers of the illness.

1.2.2 The Ultra High Risk Approach

As the prodromal phase can only be determined retrospectively, during the past decade, researchers have aimed at identifying putatively prodromal subjects by studying subjects with a high risk (HR) for developing psychosis. The first studies that investigated HR subjects mainly focussed on subjects with a genetic risk for schizophrenia, i.e. first-degree relatives of patients with schizophrenia. More recently, the focus has shifted to subjects at clinical HR. Particularly, two approaches have shown some promise in the valid and reliable identification of at risk subjects (Ruhrmann et al., 2012). First, researchers from the Early Psychosis Prevention and Intervention Centre in Melbourne Australia (McGorry et al., 2003; Yung et al., 2007) have coined the ‘Ultra High Risk’ (UHR) concept. This term refers to a subthreshold syndrome that can be regarded as a risk factor for subsequent psychosis within the next year. Psychosis is however not inevitable. The UHR approach consists of three criteria, in combination with social and occupational decline: 1) Attenuated Positive Symptoms: subjects who have experienced subthreshold, attenuated positive psychotic symptoms during the past year; 2) Brief limited intermittent psychotic symptoms: subjects who have experienced episodes of frank psychotic symptoms that resolved spontaneously within 1 week and 3) Genetic risk in combination with reduced functioning: subjects who have a first degree relative with a psychotic disorder, or who themselves have a schizotypal personality disorder and who have experienced a decrease in functioning during the past year. Second, researchers from the University of Cologne in Germany have defined the ‘Basic Symptoms’ (BS) criterion. This criterion refers to self-reported impairments in cognitive and perceptive functioning, for instance an inability to divide attention, thought interference or disturbances in receptive or expressive speech. Indeed, several studies have yielded that these subjective cognitive symptoms may have a strong predictive value for transition to psychosis over a period of 10 years (Klosterkötter et al., 2001; Schultze-Lutter, 2009).

Within UHR cohorts included using the above mentioned criteria, transition rates vary, with percentages ranging between 13 and 50% (Ruhrmann et al., 2010; Olsen & Rosenbaum, 2006). Considering subjects at UHR while they do not make a transition (the so-called false positives) may potentially lead to unnecessary fear, stigmatization and treatment (Nelson & Yung, 2010; Yung et al., 2007). Therefore, there is still a need for markers that may contribute to the differentiation between UHR subjects who will or will not make the transition to psychosis, i.e. markers that signify a risk marker of the onset of schizophrenia. Eventually, these markers may be helpful to identify...
subjects at risk for psychosis, herewith creating opportunities for early detection and intervention that aim at avoiding the transition to psychosis or ameliorating the course of psychotic disorders (Ruhrmann et al., 2012). During the past decade, researchers have already demonstrated abnormalities on neuroimaging (Job et al., 2003; Pantelis et al., 2007; Takahashi et al., 2009), neuropsychological (Brener et al., 2005; Niendam et al., 2007) and neurophysiological (Bramon et al., 2008; Frommann et al., 2008; Ozgürdal et al., 2008; van der Stelt et al., 2005) assessments in UHR subjects, possibly indicating a pre-existing vulnerability to psychosis. Numerous studies reported on the contribution of cognitive and neuroimaging markers to the prediction of a first psychotic episode (e.g. Lawrie et al., 2008; Seidman et al., 2010). However, research on the predictive value of neurophysiological abnormalities is scarce. Specifically, despite the vast body of knowledge that indicates that neurophysiological deficits are biological markers of schizophrenia, neurophysiological correlates of the UHR period and transition to a first psychosis have not been thoroughly examined yet.

1.3 NEUROPHYSIOLOGICAL PARADIGMS

Information processing deficits are a core feature of schizophrenia (Braff, 1993; Cadenhead et al., 1997). It has been hypothesized that these deficits, which may include difficulties in focussing attention and impaired suppression mechanisms, can lead to stimulus overload, cognitive fragmentation and formal thought disorder. Hereby, these impairments may severely disrupt social and professional functioning (Green et al., 2004). Information processing encompasses several stages, varying from pre-attentive rapid, to more attentive, conscious processing. With the aid of neurophysiological paradigms, attempts have been made to identify biological substrates of information processing deficits in patients with schizophrenia. These studies may help to gain insight into the pathophysiological mechanisms underlying abnormal brain function in schizophrenia and may hereby improve understanding of this high impact disease (Campanella & Guerit, 2009). Using several neurophysiological paradigms, including derivates of the electroencephalogram (EEG) and investigation of eye movements, abnormalities in brain functions in schizophrenia patients have been determined.

1.3.1 Electro Encephalogram, Evoked Potentials and Event Related Potentials

Cortical networks have a tendency to engage in oscillatory activity (Uhlhaas et al., 2008), which takes place through electrical activity of the nerve fibres and nerve cells. This activity can be picked up with an EEG in which electrodes are placed to the skull. The clinical EEG can provide information about certain brain diseases such as epilepsy and the general state of an organism (for example sleeping and waking state). Additionally, EEG measures may be useful for patient stratification and/or predicting disease status (Leiser et al., 2011). EEG spectral abnormalities have been frequently reported in schizophrenia patients (for a review: Boutros et al., 2008). Additionally, results of more recent studies cautiously suggest that resting state EEG parameters may also contribute to the prediction of transition to psychosis (Gschwandtner et al., 2009; Zimmermann et al., 2010).
In schizophrenia research, studies have particularly aimed at examining abnormalities in derivates of the EEG related to information processing. If the EEG is recorded while stimuli are presented and the EEG is averaged across the number of presentations of the stimuli, an identifiable patterns arises which consists of a number of positive (P) and negative (N) peaks. These peaks or components in the signal are called Evoked Potential (EP) or Event Related Potential (ERP). Several paradigms have been used to investigate abnormalities in these components. In this thesis, the focus will be on the ‘paired-click’ and the ‘oddball’ paradigm.

**Paired Click paradigm**

A dominant hypothesis in schizophrenia research is that schizophrenia patients are less able than healthy controls to inhibit irrelevant stimuli, leading to an overload of incoming information. A commonly used method to assess the ability to filter out irrelevant stimuli is the paired click paradigm. In this paradigm, two clicks, separated by an interval of 500 msec, are presented. Historically, this paradigm was mostly used to assess the P50; i.e. a small wave occurring about 50 msec after stimulus presentation. The P50 is believed to reflect the pre-attentive brain response to stimuli. Whereas the P50 amplitude to the first click (S1) is thought to assess the capacity of the central nervous system to register salient stimuli, the amplitude after the second click (S2) is associated with suppression of redundant and irrelevant stimuli. P50 abnormalities have been frequently reported in schizophrenia patients (Bramon et al., 2004; Patterson et al., 2008). Moreover, there is already some evidence to suggest that P50 abnormalities are already present in subjects at clinical high risk for psychosis (Myles-Worsley et al., 2004). Using the paired click paradigm, abnormalities have also been demonstrated in later ERPs, such as the N100 (Brockhaus-Dumke et al., 2008) and P200 (Boutros et al., 2004) in schizophrenia patients, suggesting that gating deficits are also present beyond the pre-attentive phase of information processing. To our knowledge, no studies have yet reported on the predictive value of sensory gating parameters for future transition to psychosis or on the course of gating abnormalities from the prodrome until after the onset of a first psychotic episode.

**Oddball paradigm**

In the oddball paradigm, subjects are asked to actively discriminate between task-relevant and irrelevant stimuli. For example, during an active auditory-oddball paradigm, participants are asked to count and / or respond to high (target) against a background of low (non-target) tones. As with the paired click paradigm, information processing during several time stages can be examined. For instance, the N100 is presumed to reflect primary and secondary auditory functions as well as alertness and motivation (Potts et al., 1998), whereas the N200 indexes cognitive processes involved in the categorization of deviant stimuli (O’Donnell et al., 1993). Using this paradigm, abnormalities in N100 and N200 components have been reported in schizophrenia patients, although findings are contradictory (van der Stelt et al., 2004; Winterer et al., 2001). One of the most frequently assessed and presumably most reliable biomarkers of schizophrenia is the P300.
The P300 is a neurophysiologic measure that is used to assess conscious, attention dependent information processing (Donchin & Coles, 1988; Kok, 2001). Reduced P300 amplitudes are one of the most replicated findings in the neurophysiological examination of schizophrenia patients (Bramon et al., 2004). Prolonged P300 latencies have also been reported, albeit this finding seems less robust. Recent studies have demonstrated smaller P300 amplitudes in UHR subjects (Bramon et al., 2008; Frommann et al., 2008; Ozgürdal et al., 2008; van der Stelt et al., 2005). As with the paired click parameters, studies reporting on the predictive value of P300 abnormalities for the development of a first psychotic episode or the longitudinal course of P300 components are lacking. Moreover, no reports are yet available on earlier components as derived from the oddball paradigm in UHR subjects.

1.3.2 Eye movements
Another frequently applied method to assess neurophysiological abnormalities in schizophrenia patients is the investigation of eye movements. Abnormal eye movements are believed to be a reflection of disturbances in neuronal circuits that are relevant in the investigation of the neurobiology of schizophrenia. In this thesis, the focus will be on two paradigms: the smooth pursuit eye movement (SPEM) task and the antisaccade test.

**Smooth Pursuit Eye Movements**
Smooth Pursuit Eye Movements (SPEM) are applied to track a moving object with the eyes while keeping that object on or near the fovea, thus enabling humans to focus on moving objects (Zanelli et al., 2005). Abnormalities on SPEM tasks, specifically a reduced gain and increased rates of saccades during pursuit, are consistently observed in schizophrenia (Holzman, 1987; Levy et al., 2000; O’Driscoll & Callahan, 2008) and have also been reported in relatives of patients with schizophrenia (Ettinger et al., 2003; Holzman et al., 1978). Therefore, eye tracking deficits have been proposed as markers for a genetic vulnerability for schizophrenia, thus as an identifier of the underlying genetic abnormalities of the disorder (Haraldsson et al., 2009; Holahan & O’Driscoll, 2005; Lee & Williams, 2000). To our knowledge, no studies have yet investigated SPEM in patients at UHR of developing a psychosis.

**Antisaccade Test**
On the antisaccade test, subjects are asked to inhibit a reflexive saccade to a suddenly appearing visual target (e.g. a red dot) and look in the opposite direction (Nieman et al., 2007). This task assesses working memory functions and volitional control associated with fronto-striatal dysfunction (Hutton & Ettinger, 2006). Since Fukushima and colleagues first reported an increased error rate on the antisaccade test in patients with chronic schizophrenia, this finding has been replicated in more than 40 studies. The mean error rate of schizophrenia patients on this task varies from 25 – 75% (Hutton et al., 2004). To the best of our knowledge, up to now, only one study examined antisaccade test performance in UHR subjects (Nieman et al., 2007), whereas no studies have yet investigated if increased antisaccade error rate contributes to the prediction of a psychotic episode and/or whether the antisaccade error rate shows changes associated with psychotic onset.
1.4 AIM AND OUTLINE OF THIS THESIS

The overall aim of the studies described in this thesis is to develop an integrative multi-system model of neurophysiologic abnormalities related to information processing associated with a first psychotic episode. More specifically, the aim of the studies included in this thesis is twofold. First, we aim to identify neurophysiological markers of schizophrenia and to investigate whether particular neurophysiologic markers can contribute to the prediction of a first psychotic episode in UHR subjects. Second, we aim at distinguishing neurophysiological antecedents of a first psychosis from its correlates and consequences, by following our UHR sample longitudinally.

**AIM I** To identify neurophysiological markers of schizophrenia and to investigate whether biological markers can contribute to the prediction of a first psychotic episode.

Chapter 2 encompasses an overview of neurophysiological abnormalities in schizophrenia patients. Specifically, derivates of the EEG, prepulse inhibition of the startle reflex and eye movement research will be addressed. Furthermore, candidate neurophysiological endophenotypes of schizophrenia are discussed. Chapter 3 focuses on determining possible eye tracking deficits in UHR subjects, by comparing performances of UHR subjects and controls on a task of smooth pursuit eye movement (SPEM). In Chapter 4, we sought to investigate whether abnormalities in P300 or other ERPs are present in UHR subjects and if they are helpful in predicting transition to psychosis. Chapter 5 describes the findings of a multi-centre study, focussing on the question if quantitative EEG measures are helpful in predicting transition to psychosis. Chapter 6 describes the findings of a longitudinal study on the auditory ERP components in UHR subjects, whereas Chapter 8 focuses on the course of sensory gating abnormalities from the prodrome until after psychotic onset. In the last Chapter of Part II of this thesis (Chapter 9) we focused on a profile of information processing deficits, using complementary neurophysiological markers, in UHR subjects as well as patients with a first episode of schizophrenia psychosis. In this chapter, we propose an integrative multi-system model of neurophysiologic abnormalities related to information processing associated with a first psychotic episode.

In the second part of this thesis, we aim at distinguishing neurophysiological antecedents of first psychosis from its correlates and/or consequences. Chapter 7 describes the findings of a longitudinal study on the auditory ERP components in UHR subjects, whereas Chapter 8 focuses on the course of sensory gating abnormalities from the prodrome until after psychotic onset. In the last Chapter of Part II of this thesis (Chapter 9) we focused on a profile of information processing deficits, using complementary neurophysiological markers, in UHR subjects as well as patients with a first episode of schizophrenia psychosis. In this chapter, we propose an integrative multi-system model of neurophysiologic abnormalities related to information processing associated with a first psychotic episode.

**AIM II** To determine the course of neurophysiological abnormalities from before until shortly after transition to a first psychotic episode.

In Chapter 10 we summarize the findings and implications of our study. Caveats of the studies described in this thesis, as well as directions for future studies will be discussed.
REFERENCE LIST


GENERAL INTRODUCTION

1

MRI temporal lobe gray matter and to other ERP abnormalities. Biol Psychiatry 34, 26-40.


