Neuropsychological correlates of the pathway to the early stages of psychosis
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REVIEW OF NEUROPHYSIOLOGICAL ABNORMALITIES IN SCHIZOPHRENIA

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1. INTRODUCTION

Information processing deficits are a core feature of schizophrenia. For instance, due to impaired selection and inhibition mechanisms, schizophrenia patients have difficulties processing stimuli from the environment. Impairments in memory and attention, e.g. the focussing of attention, have also been frequently reported. Furthermore, patients with schizophrenia, especially during the active psychotic state, show reduced planning and self-reflection abilities. Neurophysiological research can be used to study the biological substrates of these symptoms of schizophrenia. In this chapter, derivates of the electroencephalogram (EEG), prepulse inhibition of the startle reflex and eye movement research will be discussed sequentially. Furthermore, we will investigate the usefulness of these biomarkers as candidate endophenotypes of schizophrenia.

2. EEG / ERP

2.1 EEG

Information transfer in the central nervous system takes place through electrical activity of the nerve fibres and nerve cells. Changes of potentials generated on the receptive ends of the neuron (dendrites) or the cell body itself, lead to tiny electrical currents that travel along the nerve fibres (axons). The electrical activity of the brain can be recorded with electrodes on the skull. The recorded EEG signal results from volume conduction of the electrical neural activity, or more specifically from synchronous voltage fluctuations due to postsynaptic potentials throughout the cerebral cortex. The EEG is a powerful non-invasive tool with a high temporal resolution, and is therefore uniquely suited to examine rapid changes in brain activity underlying cognitive functions (van der Stelt & Belger, 2007). The spatial resolution of the EEG is low compared to other neuroimaging methods, including PET and functional MRI (Stern & Silbersweig, 2001).

The clinical EEG can provide information about certain brain diseases such as epilepsy and relates to the general state of an organism (such as sleeping and waking). The EEG is typically described in terms of rhythmic activity, which is divided into bands by frequency. These frequency bands have a certain biological significance, i.e. the frequency bands may reflect specific brain sources and functions (Duffy et al., 1989). The rhythmic activities in the resting state or spontaneous EEG are commonly subdivided into: i) delta, <4 Hz, observed in adults during slow wave sleep and babies; ii) theta, 4-7 Hz, seen normally in young children and in drowsiness. It is associated with relaxed, meditative states; iii) alpha, 8-13 Hz, one of the most prominent EEG phenomena and associated with relaxed wakefulness. It emerges with closing of the eyes and with relaxation, and attenuates with eye opening or mental exertion and is most prominent over the occipital regions (Uhlhaas et al., 2008). Peak alpha frequency (PAF) corresponds to the discrete frequency with the highest magnitude within the alpha range (Angelakis et al., 2007). The frequency of this oscillation has been associated with mental performance (Klimesch, 1999); iv) Beta, 13-30 Hz, most evident on frontal scalp positions and closely linked to motor behaviour.
EEG spectral abnormalities have been frequently reported in schizophrenia patients (for a review: Boutros et al., 2008). Specifically, excess of quantitative EEG (QEEG) slow wave (delta and theta) may be viewed as a robust sign of schizophrenia (Boutros et al., 2008). This finding has been replicated in both medicated and unmedicated schizophrenia patients. A decrease in alpha power, predominantly on frontal scalp positions, has also been reported (Wuebben & Winterer, 2001). Moreover, there is some evidence of EEG alpha asymmetry in schizophrenia, i.e. significantly greater left lateralized alpha power in schizophrenia patients than controls (Gordon et al., 2010).

2.2 Event Related Potentials
It is also possible to register the EEG as a reaction to the presentation of certain stimuli, and so mapping information processing. By using time domain analyses and averaging the EEG activity following multiple stimulus repetitions an identifiable pattern arises which consists of a number of positive and negative peaks (van der Stelt & Belger, 2007). These peaks or components in the signal are called Evoked Potential (EP) or Event Related Potential (ERP). To distinguish task-related activities from background spontaneous activities, a considerable number of repetitions of the stimulus is necessary for improving the signal noise ratio.

EP and ERP component are distinguished in polarity (positive and negative) and in time of occurrence (latency). Latency reflects the stage of information processing, i.e. the timing when most of the neuronal populations are activated. The amplitude reflects the amount of neuronal activity involved in the process. With respect to the latency, ERP components can be broadly subdivided into early sensory evoked potentials and later cognitive potentials. The early components (i.e. EPs) emerge in the first 100 ms after stimulus presentation. An example of the EP is the P50, a positive wave that occurs about 50 msec after stimulus presentation. It is assumed that this early component is a reflection of a pre-attentive mechanism, where no conscious information processing is needed. The later (i.e. > 150 ms) components are believed to reflect higher order, cognitive processing. In this chapter a number of EPs and ERPs in which abnormalities are frequently observed in schizophrenia patients will be discussed.

2.2.1 Sensory gating: P50
Our nervous system is constantly bombarded with incoming information. The first screening of stimuli from the environment occurs during the pre-attentive phase of information processing, in which relevant and irrelevant stimuli are differentiated. A central hypothesis in schizophrenia research is that schizophrenia patients are unable to inhibit irrelevant stimuli or select relevant stimuli, leading to an overload of incoming information. A widely used neurophysiological measure in assessing pre-attentive auditory information processing is the P50, a small wave occurring about 50 msec after stimulus presentation. The P50 is an auditory evoked potential (AEP), i.e. a scalp EEG measure of the pre-attentive
brain response to stimuli. A commonly used method to assess the P50 is the paired click paradigm in which two clicks, separated by an interval of 500 msec, are presented. The P50 amplitude to the first click (S1) is thought to assess the capacity of the central nervous system to register salient stimuli, whereas the amplitude after the second click (S2) is associated with suppression of redundant and irrelevant stimuli. In healthy control subjects, the P50 amplitude after S2 is usually approximately 80% smaller compared to the S1 amplitude, reflecting a selection method that protects the brain against redundant information (Bramon et al., 2004a). An example of grand average wave forms for S1 and S2 stimuli of schizophrenia patients and healthy controls is presented in Figure 1.

The P50 ratio, i.e. the P50 amplitude after S2 divided by the S1 amplitude, is usually smaller in healthy control subjects compared to patients with schizophrenia. In a recently published meta-analyses, it was reported that the P50 ratio was higher in schizophrenia patients than controls in 45 of the 46 included studies (Patterson et al., 2008). Another meta-analyses described an increase of the P50 ratio of 1.56 SD in schizophrenia patients (Bramon et al., 2004a). These findings suggest that schizophrenia is associated with dysfunctional inhibitory mechanisms: patients with schizophrenia are less able than healthy control subjects to filter irrelevant stimuli.

An elaborate neuronal circuitry is believed to underlie the sensory gating impairments in schizophrenia (Thaker, 2008). Whereas temporo-parietal and prefrontal cortical areas are involved in the early phase of sensory processing, hippocampal areas are believed to play a pivotal role in the subsequent phases of gating. The reduced P50 suppression for S2 is thought to be a reflection of neuronal hyper-excitability, occurring as a result of defects in cortical and subcortical inhibitory mechanisms. The inhibitory interneurons in the CA3 and CA4 of the hippocampus are believed to play an important role in these selection processes. Through cholinergic innervations, the medial septal nucleus mediates the sensory response of the hippocampus. Both genetic, physiologic and pharmacologic studies have demonstrated that nicotine receptors are essential here (Griffith et al., 1998; Potter et al., 2006). The hypothesis that nicotine is closely involved in P50 gating is also supported by the finding that a high dose of nicotine may normalize the P50 in schizophrenia patients and their relatives (Potter et al., 2006). In contrast, nicotine use may diminish P50 sensory gating in healthy controls (Brinkmeyer et al., 2011).

P50 abnormalities have also been observed in studies in relatives of schizophrenia patients, suggesting a possible genetic component in the P50 abnormalities (Thaker, 2008; Turetsky et al., 2007). With regard to the underlying genotype, amongst others, associations between P50 abnormalities and changes in the chromosome locus15q14 have been described (Freedman et al., 1997). Associations studies have also implicated the alfa, nicotine receptor gen in sensory gating impairments (Thaker, 2008).

The above mentioned findings suggest that the P50 may be viewed as a reliable biological marker of schizophrenia. However, several studies have questioned the reliability of this measure. First, the variability of the P50 amplitude is high, also in healthy control subjects. For instance in a study analysing 84 studies on the P50 component in schizophrenia, it was demonstrated that the P50 ratio of 40% of the healthy control
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...subjects was within the range of the schizophrenia subjects (Potter et al., 2006). Second, the P50 abnormalities have not been replicated in all studies in schizophrenia subjects. This may be due to differences between research groups in methodology. For instance, there is an ongoing debate regarding the effects of the use of high- or low pass filters, click intensity and duration, stimulus presentation methods and peak detection methods (de Wilde et al., 2007). Before these issues are resolved, no firm conclusions with respect to the P50 as a marker of schizophrenia can yet be drawn.

P50 abnormalities are not specific to schizophrenia. For example, reductions in S2 suppression have also been reported in patients with a bipolar disorder and cocaine users (Thaker, 2008). However, in schizophrenia patients the P50 abnormalities often persist after remission of the disease, whereas the P50 ratio normalizes in patients with a bipolar disorder and cocaine users after remission or cessation of use.

2.2.2 Prepulse inhibition of the startle response

Prepulse inhibition (PPI) is an operational measure of sensorimotor gating. On a conceptual level, sensorimotor gating is comparable to the sensory gating (P50), because it protects an individual from an overload of incoming sensory information. Sensorimotor gating is usually investigated with the startle reflex, a defensive motor reaction that consists of the contraction of particular muscles or muscle groups after the presentation of an unexpected stimulus (e.g. visual, auditory of tactile). In healthy subjects, the startle amplitude is usually reduced if this stimulus is preceded by a mild (prepulse) stimulus presented 30–500 ms prior to the startling stimulus. The PPI is frequently expressed as the percent reduction of the startle amplitude between prepulse trials and pulse-alone trials (Maier et al., 2008).

During the past few decades, many studies have demonstrated that schizophrenia patients show reduced prepulse inhibition, whereas the startle reflex itself is not deviant from healthy controls (Braff et al., 2001). The PPI is believed to be a stable marker that most likely reflects a vulnerability to the disease (Swerdlow et al., 2008). The heritability of the PPI is estimated between 32 and 50%. Moreover, different studies have revealed associations between the PPI and dopamine as well as serotonin related genes (Anokhin et al., 2003). Specifically, the serotonin-2A receptor (5-HT(2A)R) and the T102C genotype have been implicated in both the pathogenesis of schizophrenia and the PPI deficits of schizophrenia patients (Quednow et al., 2008). Finally, several cortical and subcortical regions are involved in the inhibition of the startle response. Moreover, an elaborate limbic cortico-striato-pallido-thalamic circuitry is involved in the mediation of the pulse response.

Reduced prepulse inhibition is not specific to schizophrenia. PPI reductions are also observed in other neuropsychiatric disorders, including obsessive compulsive disorder, bipolar disorder, ADHD and Huntington’s disease. A common feature of these disorders is the involvement of the limbic cortico-striato-pallido-pontine circuit, a circuit that is, as discussed above, believed to be involved in the PPI. PPI abnormalities are also observed in Velocardiofacial Syndrome (VCFS) (Vorstman et al., 2008), a disease that may represent one of the highest known risk factors to schizophrenia. VCFS is
a congenital, autosomal dominant condition. In most patients, microdeletions at chromosome 22q11.2 are responsible for the syndrome. There is a high co-morbidity of VCFS and psychiatric disorders. For example, approximately 30% of the patients with VCFS develop a psychotic episode during adolescence (Murphy & Owen, 2001).

2.2.3 Mismatch Negativity

Mismatch negativity (MMN) is a negative ERP component that occurs after the presentation of a deviant stimulus, i.e. the ‘oddball’ stimulus, presented against a background of repetitive stimuli. The oddball stimulus may differ from the standard stimuli in various dimensions, including duration, frequency and intensity. The MMN is a reflection of the response that occurs after the detection of stimulus change and represents the involuntary switch of attention to the deviant stimulus. The MMN typically occurs between approximately 150 and 250 msec after presentation of the oddball stimulus and has its maximum at fronto-central scalp positions (Rissling & Light, 2010).

Although the MMN may vary by attentional abilities or over different task situations, the MMN is thought to reflect involuntary attentional processes. Therefore, no conscious processing or motivation is required. The MMN is usually elicited by presenting tone sequences, while the subject is engaged in another task, e.g. reading a book. The MMN can also be recorded in patients during sleep or coma. Herewith, the MMN is an ideal measure of the neural substrates underlying auditory discrimination and involuntary attention.

Using neuroimaging studies, it has been demonstrated that the MMN is generated in the primary and secondary auditory cortex. Moreover, Heschl’s gyrus, which is located in the temporal lobe, is involved in the generation of this component, with possible additional generating sources in the frontal lobes (van der Stelt & Belger, 2007). Evidence is growing that MMN may be a reflection of the N-Methyl-D-aspartic acid or N-Methyl-D-aspartate (NMDA) receptor function (Kenemans & Kahkonen, 2011). NMDA is an amino acid derivative, which acts as a specific agonist at the NMDA receptor mimicking the action of glutamate. Different studies have shown that NMDA is involved in the MMN. For instance, ketamine (a NMDA antagonist) reduced the MMN amplitude in healthy controls. Smaller MMN amplitudes are also associated with the psychotic symptoms that may occur after ketamine usage. Although associations of MMN with catechol-O-methyltransferase (COMT) have been described, the precise genetic basis of MMN is still poorly understood.

The MMN can usually be reliably assessed: the test-retest reliability is good. Up to now, at least 40 studies have reported on MMN abnormalities in schizophrenia patients. In a meta-analysis of 32 MMN studies in schizophrenia, it was concluded that schizophrenia patients consistently demonstrate reduced MMN amplitudes after frequency or duration deviant stimuli (Umbricht & Krljes, 2005). Schizophrenia patients especially show smaller MMN amplitudes after the presentation of duration deviant oddball stimuli, implying that schizophrenia patients are less able than controls to discriminate stimulus duration. Although less consistent, abnormalities have also been reported after the presentation of stimuli that deviate from the standard stimuli with respect to frequency or pitch. In the meta-analysis of Näätänen and Kähkönen (2009), a clear effect of disease duration on
the MMN amplitude was reported, in particular regarding the duration deviant stimuli. These findings suggest that reduction of the MMN amplitude may be a reflection of disease progression. The absence of MMN abnormalities in patients with a first episode of schizophrenia is in accordance with this hypothesis (Rissling et al., 2010).

Several studies yielded that deficits in early auditory processing, specifically MMN abnormalities, may contribute to poor social cognition and community functioning in schizophrenia patients. For instance, MMN reductions have been related to impairments in psychosocial functioning and social cognition (Hermens et al., 2010), where associations seem to be most pronounced with functional domains like work and independent living (Wynn et al., 2010).

It has been estimated that MMN amplitudes have a heritability of 60% (Umbricht & Krljes, 2005). In accordance, MMN abnormalities have also been reported in relatives of schizophrenia patients. There are no evident effects of medication on the MMN (Kasai et al., 2002; Naatanen & Kakhonen, 2009). MMN abnormalities have been demonstrated in both medication free subjects and schizophrenia subjects who use anti-psychotic medication. Although in some studies it was concluded that MMN abnormalities are specific for schizophrenia (Umbricht et al., 2003), MMN abnormalities have also been demonstrated in patients with bipolar disorders (Jahshan et al., 2012) and major depressive disorder (Kaur et al., 2011).

### 2.2.4 P300

In contrast to the ERPs that were discussed above, the P300 is a neurophysiologic measure that is thought to assess conscious, attention dependent information processing. It is a relatively slow, low-frequency neuroelectrical event that is maximal to task relevant stimuli and absent to task irrelevant stimuli (van der Stelt & Belger, 2007). Specifically, two subcomponents of the P300 can be distinguished (Squires et al., 1975). The P3a potential, which typically reaches its maximum at frontal electrode positions, is thought to reflect automatic initial processing when a novel or distracting stimulus is detected, whereas the following parietal maximal P3b is believed to be a reflection of subsequent effortful attentional resources, associated with updating task-relevant information in memory (Demiralp et al., 2002; Donchin & Coles, 1988; Kok, 2001). The P3 components are frequently elicited using an active auditory-oddball paradigm. In this task, participants are asked to count and respond to high-pitched tones (targets) against a background of low-pitched tones (non-targets).

The P3b (from here referred to as ‘P3’) is a frequently applied measure in studies assessing information processing in different psychiatric diseases. The first study reporting on the P3 has appeared more than 40 years ago. Although P3 abnormalities have been reported in a variety of disorders, including dementia, traumatic brain injury, ADHD and autism (Duncan et al., 2009), P3 amplitude reductions are most consistently reported in schizophrenia (Bramon et al., 2005). Reduced P3 amplitudes and prolonged P3 latencies are one of the most replicated findings in the neurophysiological examination of schizophrenia patients. The test-retest reliability of the P3 amplitudes is high. Although prolonged P300 latencies, indicating a reduced speed of information
processing, have also been frequently reported, latency prolongations are a less reliable measure of cognitive impairments in schizophrenia.

There is some evidence that P3 amplitude abnormalities are related to state factors of the disease, e.g. fluctuations in psychotic symptoms, suggesting that the P3 may be a state marker of the disease. However, P3 abnormalities are also reported in schizophrenia patients in remission. Moreover, P3 amplitude reductions have also been documented in patients with a schizophrenia spectrum disorder as well as in relatives of schizophrenia patients and in subjects with a high risk for developing psychosis (Frommann et al., 2008; van Tricht et al., 2010b), implying that the P3 may in fact be related to the aetiology of the disease, thus reflecting a trait marker of schizophrenia (Blackwood, 2000). Another study yielded both state and trait aspects of P3 amplitude reductions in schizophrenia (Mathalon et al., 2000). Twin studies have demonstrated that both P3b latencies and amplitudes are (partly) hereditary. In a meta-analysis it was concluded that P3 amplitudes are genetically determined for 60%, whereas genetic factors explained 51% of the variety in P3 latencies (van Beijsterveldt et al., 2001). The reported differences in heritability rates are most likely due to variations in task paradigm, scalp position or stimulus modality. For example, the visual P3 often fluctuates with variations in clinical symptoms whereas the auditory P3 seems a more stable marker of schizophrenia (van der Stelt & Belger, 2007).

The cerebral origin of the P3 is not yet completely understood. It involves the complex summation of activity of multiple brain regions, particularly various association areas of the cerebral cortex and the limbic system (van der Stelt & Belger, 2007). The molecular genetic basic of the P3 is to date largely unknown. Several dopamine related genes are thought to influence the P3. Linkage has been reported at several chromosomal locations to P3 abnormalities in schizophrenia. Blackwood and colleagues (Blackwood et al., 2001) investigated the P3 in a large family with high rates of schizophrenia and with a balanced translocation of chromosome 1 and chromosome 11. This translocation disrupts the gene Disrupted in Schizophrenia 1 (DISC1) on chromosome 1q42, an abnormality that has been linked to the aetiology of schizophrenia. In this study, it was demonstrated that in relatives carrying the translocation, P3 amplitudes were smaller compared to relatives without this translation and healthy control subjects. Reduced P3 amplitudes were also observed in relatives with a translocation but without psychiatric symptoms. These findings suggest that reduced P3 amplitude may be a reflection of DISC1 genetic vulnerability. Additionally, associations between the auditory P3 and catechol-O-methyltransferase (COMT), a gene that is also associated with schizophrenia vulnerability, has been demonstrated in some but not all P3 studies.

A confounding factor that needs to be addressed in the P3 research is the use of psychoactive medication, specifically the effect of antipsychotic medication. Until now, there is no consensus about the relationship between medication and P3 amplitudes. Although P3 amplitude reductions have also been observed in medication free schizophrenia subjects, there is some evidence that specific antipsychotic medication (i.e. olanzapine) may enhance P3 amplitudes (Bramon et al., 2004b; Mathalon et al., 2000). However, P3 amplitudes are generally not restored to normal levels (Hirayasu et al., 1998; Jeon & Polich, 2003).
3. EYE MOVEMENTS

In addition to the assessment of EEG and ERPs, another frequently applied method to measure information processing in schizophrenia patients is the assessment of eye movements. Abnormal eye movements are believed to be a reflection of disturbances in neuronal circuits that are relevant for the neurobiology of schizophrenia.

3.1 The antisaccade test

During the antisaccade test, subject 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). It has been frequently reported that schizophrenia patients have more difficulties on this task compared to healthy controls (Nieman et al., 2000). Since Fukushima and colleagues (1988) 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 (Hutton & Ettinger, 2006). Average antisaccade error rates in healthy humans vary, but recent studies suggest a mean error rate of 20%. The mean error rate of schizophrenia patients on this task varies from 25 – 75 % (Hutton et al., 2004). High error rates have also been reported in patients with recent onset schizophrenia and medication free schizophrenia subjects. Thus, the increased error rate can most likely not be explained by disease duration or medication effects and may therefore be considered as a trait marker of the disease. As with EEG and ERP measures, antisaccade abnormalities are not specific to schizophrenia; increased error rates have also been reported in other psychiatric disorders, including affective disorder, ADHD, obsessive compulsive disorder and autism.

Reduced inhibitory control of the dorsolateral prefrontal cortex (DLPFC) is believed to underlie the suboptimal performance on the antisaccade test. This neural substrate is involved in the inhibition of reflexive behaviour and higher cognitive functions important for complex problem solving skills. The DLPFC is also an important neural substrate for working memory functions. Moreover, different studies have demonstrated that an increased error rate on the antisaccade test is related to a worse performance on tasks of working memory, further supporting the importance of the DLPFC in the antisaccade task performance. In a recent study on antisaccadic eye movements in schizophrenia patients and first-degree biological relatives of schizophrenia patients, it was demonstrated that both schizophrenia patients and their relatives tended toward increased activity over orbital frontal cortex prior to saccades. In addition, increased error rates have been reported in patients with lesions in the frontal lobe (Kang et al., 2011). These findings are consistent with theory of lateral prefrontal dysfunction underlying deficient saccadic control.

The error rate on the antisaccade test is not constant over life. The error rate is the highest during childhood, whereas young adults perform relatively well on this task. After this life phase, the error rate slowly increases to the age of 60, after which a rapid increase occurs. Thus, the variations in antisaccadic test performance seem to largely reflect the developmental trajectory of the frontal lobe.
In a study investigating a large sample of mono- and dizygotic twins, the heritability of the antisaccadic error rate has been estimated on 57% (Ettinger et al., 2006). Moreover, in a meta-analysis on the antisaccadic error rate in relatives of schizophrenia, it was concluded that as compared to healthy control subjects, relatives of schizophrenia patients also show reduced performance on this task (Levy et al., 2004). Many attempts have been made to investigate the genotype underlying the suboptimal performance on the antisaccade test. In a study in eight families of schizophrenia patients, a relationship between the error rate and chromosome locus 22q 11-12 was reported. Although this findings needs to be replicated, it is worth noting because the catechol-O-methyltransferase (COMT) gene is located in the associated area. The COMT gene catalyzes dopamine. Moreover, the val(158)met single nucleotide polymorphism (rs4680) in the COMT gene has received considerable attention as a candidate gene for schizophrenia as well as for frontally mediated cognitive functions (Haraldsson et al., 2009).

3.2 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 an individual to focus on moving objects (Zanelli et al., 2005). Abnormalities in SPEM are usually assessed by determining the ability of an individual to follow a moving stimulus, e.g. a red dot. Quantitative parameters for SPEM task performance are diverse and may include the smooth pursuit gain and the saccadic rate. SPEM gain is defined as the ratio between target velocity and eye velocity. A pursuit response gain of less than one or higher than one means that pursuit velocity is less than target velocity or higher than target velocity, respectively. With respect to the saccades, there are several types of saccadic movements that may intrude on pursuit. Usually, a differentiation is made between saccades that correct for SPEM deficiencies (corrective saccades) and saccades that disrupt tracking (non-corrective saccades) (van Tricht et al., 2010a).

SPEM abnormalities are consistently observed in schizophrenia patients (Holzman, 1987; Levy et al., 2000; O’Driscoll & Callahan, 2008). A lower pursuit gain and increased rates of corrective and non-corrective saccades have been frequently reported (Kathmann et al., 2003; Lee & Williams, 2000). Relatives of patients with schizophrenia also show SPEM impairments (Ettinger et al., 2003; Holzman et al., 1978; Hong et al., 2006). Therefore, eye tracking deficits have been proposed as markers of 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). Indeed, SPEM dysfunction has been associated with schizotypic symptoms, which are genetically related to schizophrenia, in schizophrenia patients and in subjects from the general population (van Kampen & Deijen, 2009). However, studies on the heritability of SPEM deficits have yielded inconsistent results. Although some aspects of SPEM are also deviant in relatives of schizophrenia patients, these relatives do not present with evident impairments in all SPEM component measures. Both a lower gain and an increased rate of anticipatory saccades have been demonstrated however, suggesting a partial genetic control of global smooth pursuit (Calkins et al., 2008).
With respect to the underlying genotype, some studies have demonstrated an association between SPEM deficits and the COMT gene on the 22q11 locus, a gene that has been frequently implicated as a candidate gene for schizophrenia. However, other studies found no evidence of an involvement of this gene in SPEM (Park et al., 2009). Additional reports on genes involved in SPEM have demonstrated that D3 (DRD3) gene located on chromosome 3q may be involved. Moreover, there is some evidence of an association between the chromosome 1q25 cytosolic PLA2 (cPLA2) gene and the haplotype RANBP1-ht2 and the risk of SPEM abnormalities (Cheong et al., 2011). Finally, although neuregulin 1 (NRG1) on 8p12, has been frequently implicated as a candidate gene for schizophrenia, no association between variants in this gene and SPEM abnormality in patients with schizophrenia could be demonstrated (Kim et al., 2012; Park et al., 2009). Thus, the genotype underlying SPEM deficits in schizophrenia patients remains unclear.

Deficits in SPEM seem to be independent of the clinical status of schizophrenia patients: similar results are found in the acute phase of the disease and in remission (Kallimani et al., 2009). Moreover, SPEM abnormalities have been reported in subjects at high risk for psychosis (van Tricht et al., 2010a). These findings suggest that SPEM abnormalities may also be viewed as a trait marker of schizophrenia.

The underlying cerebral mechanism of SPEM is complex; many cortical and subcortical areas are involved (for an overview see Leigh & Zee, 2006; Lencer & Trillenberg, 2008). The medial superior temporal (MST) area of V5 plays an important role in the initiation, generation and maintenance of SPEM (Lencer et al., 2004; Nuding et al., 2008). In addition, frontal areas, including the frontal eye fields (FEF), the supplementary eye field (SEF), the prefrontal and the premotor cortex and the anterior cingulate are crucial in SPEM performance. The FEF are thought to be involved in anticipating and predicting the stimulus movement in predicatively moving stimuli (Leigh & Zee, 2006; Nagel et al., 2008), and through inhibition of the superior colliculus in suppressing non-purposive saccades (Shaffer et al., 2003), whereas other frontal areas are responsible for suppressing unwanted saccades, learning and motor planning (Lencer & Trillenberg, 2008). Parietal areas have also been proposed to be related to the suppression of saccades during pursuit (Lencer & Trillenberg, 2008) and SPEM deficits have also been associated with disinhibited hippocampal activity (Tregellas et al., 2004). Finally, the basal ganglia are an important source in the control of non-reflexive saccades, for example by inhibiting the superior colliculus (Shaffer et al., 2003).

Although SPEM abnormalities are one of the most replicated findings in schizophrenia patients, SPEM impairments are not specific to schizophrenia. For instance, SPEM abnormalities have also been documented in patients with bipolar disorder (Martin et al., 2011), alcoholism (Bauer, 1997) and in patients with multiple complex developmental disorder (MCDD; Lahuis et al., 2009). However, it has been postulated that SPEM dysfunctions may be more common in schizophrenia compared to acutely manic patients (Amador et al., 1991). Moreover, although both schizophrenia and affective disorder patients may demonstrate lower pursuit gain, a higher catch-up saccade rate in schizophrenia as compared to depressed patients and healthy controls.
has been documented. It was therefore suggested that higher rates of catch-up saccades in smooth pursuit are specific to schizophrenia (Flechtner et al., 1997).

In sum, although SPEM dysfunctions are consistently observed in schizophrenia patients, SPEM deficits are not a specific marker of schizophrenia: SPEM abnormalities are also observed in other psychiatric disorders, including affective disorders, alcoholism and MCDD. Thus, there is no evidence for diagnostic specificity of SPEM measures (Kathmann et al., 2003). Nevertheless, the rate of catch-up saccades might provide some diagnostic specificity. Future studies should assess the potential usefulness of this measure as a biological marker of schizophrenia. The comparability of SPEM results across different research groups is confounded by differences in applied methodology. For instance, smooth pursuit tasks vary on the predictability of target motion, the velocity of the target the degrees of and the visual angle spanned. Therefore, future studies should also aim at assessing pursuit functions using similar research methods.

4. ENDOPHENOTYPES

As the search for schizophrenia genes related to the clinical phenotype (i.e. observable symptoms of schizophrenia) has yielded inconsistent results, the focus of schizophrenia research has shifted to the endophenotypes, i.e. intermediate markers of high-level symptom presentation and low-level genetic variability (Greenwood et al., 2007). Endophenotypes reflect the vulnerability of an individual for the development of a certain disorder. As endophenotypes are relatively simple, well defined and measurable, it is assumed that they are determined by less genes than the complex phenotype of schizophrenia. Hereby, these endophenotypes can help to disentangle the complex phenomenology of schizophrenia.

Several criteria must be fulfilled in order for a biomarker to be called an endophenotype. First, the endophenotype should be associated with illness in the general population. Second, it should be heritable. Third, it should be a trait marker (temporal stability) and not a state marker (fluctuating with symptom changes). Fourth, it should be present in clinically unaffected subjects with an increased risk

Table 1 Candidate endophenotypes of schizophrenia

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Heritability estimates</th>
<th>Linkage findings</th>
<th>Associated gene</th>
<th>Clinical Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>P50</td>
<td>44%</td>
<td>15q14</td>
<td>Alfa7-nicotinereceptor</td>
<td>Positive symptoms</td>
</tr>
<tr>
<td>PPI</td>
<td>32-50%</td>
<td>22q11</td>
<td>NRG1</td>
<td>Positive symptoms</td>
</tr>
<tr>
<td>MMN</td>
<td>60%</td>
<td></td>
<td></td>
<td>Negative symptoms; poor functioning</td>
</tr>
<tr>
<td>P300</td>
<td>51-60%</td>
<td>1q42</td>
<td>DISC1; COMT</td>
<td></td>
</tr>
<tr>
<td>Antisaccade</td>
<td>57%</td>
<td>22q11-12</td>
<td>COMT</td>
<td></td>
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<tr>
<td>SPEM</td>
<td>70-90%</td>
<td></td>
<td>COMT</td>
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Abbreviations: PPI = prepulse inhibition; MMN = mismatch negativity; SPEM = smooth pursuit eye movements.
for the disease, for instance patients with (traits of) a schizotypical personality disorder or relatives of schizophrenia patients. An overview of frequently examined psychophysiological endophenotypes is presented in Table 1. Although some of the discussed neurophysiological measures may be useful to fill the gap between the gene and the clinical expression of the disease (i.e. phenotype), future studies are needed to for example test the stability of these biomarkers across different stages of the disease and to further delineate associated genomic and neuro-anatomic networks.

5. DISCUSSION

The aim of this manuscript was to provide an overview of neurophysiological abnormalities in schizophrenia patients. We have discussed several neurophysiological paradigms in which schizophrenia patients show deficits. Our review of studies on early information processing yielded that schizophrenia patients may show impairments in the filtering of irrelevant stimuli, reflected by deficits in sensory motor (reduced PPI) and P50 sensory gating. However, some questions regarding the reliability of these measures, in particular the P50, remain unanswered. Nevertheless, it is hypothesized that nicotine receptors and the limbic corticostriato-pallidopontine circuit are involved in these dysfunctions. Other information processing measures related to attention and orienting functions, including the MMN, are also frequently affected in schizophrenia, specifically in patients with chronic schizophrenia. MMN impairments have been related to NMDA receptor dysfunction and problems in social and professional functioning.

With regard to the ERP components related to higher order information processing, the P300 is one of the most consistent and well replicated cognitive markers of schizophrenia. Amongst others, this measure is thought to reflect one’s ability to update information in working memory. These impairments may also be related to the clinical phenotype of schizophrenia. For instance, it has been hypothesized that these deficits can lead to stimulus overload, cognitive fragmentation and formal thought disorder (Cadenhead et al., 1997; Braff, 1993).

With regard to the eye movement paradigms, schizophrenia patients demonstrate impairments on tasks of smooth pursuit eye movements as well as antisaccade tests. SPEM impairments include reduced gain as well as increased saccadic rates. Moreover, as reflected by higher antisaccade error rate, schizophrenia patients show impairments in inhibiting an unwanted response to stimuli. One of the neurobiological substrates of these impairments is the DLPFC, which has been related to higher-order cognitive function including working memory, planning and volitional control.

We also presented a brief overview on studies related to endophenotypes of schizophrenia, i.e. markers that are intermediate to the phenotype and underlying genotype. These markers may help to unravel the pathophysiological mechanisms and vulnerability genes underlying schizophrenia, hereby creating possibilities for new treatment options (Gottesman & Gould, 2003). Some of the investigated neurophysiological abnormalities reported in schizophrenia are stable over time,
unrelated to state factors and present in non-affected relatives of schizophrenia patients, implying a genetic origin of these abnormalities. We also presented results of studies demonstrating that psychophysiological measures may contribute to the understanding of the diverse clinical presentations or syndromes of schizophrenia. Thus, some psychophysiological deficits may implicate a vulnerability for the development of the negative syndrome type, whereas other markers may be related to the psychosis phenotype. To summarize, although studies demonstrated the usefulness of some biological markers as endophenotypes, future studies in large samples should be conducted to investigate the validity and relevance of these candidacy markers.

There are limitations to psychophysiological studies in schizophrenia patients. First, until the associations between neurophysiological activity and clinical phenomena including thoughts and beliefs are better understood, psychophysiological studies remain correlational and not causal. Second, results of neurophysiological studies in schizophrenia subjects may be biased by medication use, specifically antipsychotics. Moreover, it is not yet possible to use psychophysiological paradigms for diagnostic purposes. However, during the past years, researchers worldwide are studying the usefulness of biological markers in predicting transition to psychosis in high risk subjects. These studies may contribute to identifying subjects at risk for developing psychosis and may improve the possibilities for early intervention, using for example cognitive behavioural therapy. Finally, none of the discussed neurophysiological abnormalities are specific to schizophrenia. Schizophrenia is probably composed of several syndromes with a diverse biological substrate. These syndromes probably show overlap with other psychiatric disorders (e.g. bipolar disorder) as the neurophysiological deficits found in schizophrenia patients are not specific for the disease. With the appearance of the DSM-V in the (near) future, researchers worldwide are discussing the validity of classification system currently used for clinical purposes. Possibly, the biological markers related to information processing may aid in developing more valid classificatory systems.
REFERENCE LIST


Duncan,C.C., Barry,R.J., Connolly,J.F., Fischer,C., Michie,P.T., Näätänen,R., Polich,J.,


disorder and schizophrenia. Bipolar Disorders 14, 239-248.


Uhlhaas, P.J., Haenschel, C., Nikolic, D. and Singer, W., 2008. The Role of Oscillations
and Synchrony in Cortical Networks and Their Putative Relevance for the Pathophysiology of Schizophrenia. Schizophr Bull 34, 927-943.


van Kampen, D. and Deijen, J., 2009. SPEM dysfunction and general schizotypy as measured by the SSQ: a controlled study. BMC Neurology 9, 27.


