Heterogeneity in the underpinnings of the psychosis spectrum: Event-related potentials and executive functions

PhD Thesis

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LIST OF ABBREVIATIONS

AH: auditory hallucinations

ANCOVA: repeated measures analysis of covariance

ANOVA: analysis of variance

BD: bipolar affective disorder

BSNIP: Bipolar and Schizophrenia Network for Intermediate Phenotypes

CC: completed categories

CLR%: percentage of conceptual level responses

dMMN: mismatch negativity elicited by duration deviant tones

DSM: Diagnostic and Statistical Manual of Mental Disorders

ERP: event related potential

FMS: failure to maintain set

HC: healthy controls

ICD: International Classification of Diseases

MADRS: Montgomery-Åsberg Depression Rating Scale

MINI: Mini International Neuropsychiatric Interview

MMN: mismatch negativity

PANSS: Positive and Negative Syndrome Scale

PE%: percentage of perseverative errors

pMMN: mismatch negativity elicited by pitch/frequency deviant tones

S1: first stimulus

S2: second stimulus

SCID: Structured Clinical Interview for DSM-IV

SOA: stimulus-onset asynchrony

SPSS: Statistical Package for Social Sciences

SZ: schizophrenia

UHR: ultra-high risk

WCST: Wisconsin Card Sorting Task

YMRS: Young Mania Rating Scale

BRIEF SUMMARY

This thesis aims to investigate the validity of some selected candidate psychosis endophenotypes and through these the possibility of a psychosis spectrum including schizophrenia (SZ) and bipolar affective disorder with psychotic features (BD+). These two mental disorders show several overlapping symptoms and aetiological factors, although the results are ambiguous. Proper diagnosis, or rather clinical description enables appropriate interventions and might prevent frequent relapses. The identification of heritable characteristics influencing symptom development (intermediate phenotypes aka endophenotypes) is essential in creating diagnostic categories. Schizophrenic patients show severe cognitive deficits and information processing dysfunction, while these are not convincingly underpinned in bipolar affective disorder. As both syndromes might result in psychotic symptoms it was assumed that both patient groups will show similar differences compared to healthy control subjects. We wanted to investigate whether these mental disorders constitute a psychosis dimension. Based on the literature auditory event-related potentials (ERPs) and executive functions are among the most promising candidate endophenotypes, therefore we administered electrophysiological and neuropsychological paradigms proven to be appropriate measures of the aforementioned dysfunctions.

In Study I we registered five auditory event-related potentials (P50 and N100 suppression, duration and pitch deviant mismatch negativity – dMMN, pMMN and P3b) representing different stages of auditory stimulus procession. Twenty patients with SZ, N=20 with BD+ and N=21 healthy control (HC) subjects were involved. The results suggest profound differences among the groups; therefore they do not support the notion of the dimensional approach of psychotic disorders. SZ patients demonstrated N100 suppression deficit, shortened dMMN latency and smaller P3b amplitude. In the group with BD+ the only significant difference from HC was the prolonged latency of pMMN. Though ERPs were registered in the same laboratory setting we could not find common ERP deficits in SZ and BD+ groups.

In Study II different aspects of executive functions were examined by the means of Wisconsin Card Sorting Task (WCST) in SZ (N=26), BD+ (N=24) and HC (N=21) groups.

Schizophrenic patients showed disrupted set-shifting and conceptualization ability, while the BD+ group did not differ significantly from the HC. These results indicate different patterns of cognitive dysfunctions in SZ and BD+.

The correlations of demographic and clinical variables with the measures of WCST and the involved ERPs were also analysed. N100 suppression deficit and the frequency of failure to maintain set during WCST are interrelated, which indicates the role of early stimulus screening in sustaining adaptive behaviours. Correlations between clinical symptom severity and characteristics of P50 suppression and P3b were revealed mainly in the BD+ group: unattended and conscious auditory screening processes are both more dysfunctional by patients with more severe clinical symptoms. As clinically stable patients were included in both studies this indicates the role of basic neurophysiological deficits in symptom development.

According to our results we failed to find common endophenotypes for SZ and BD+ using auditory ERPs and the WCST contradicting the notion of a common psychosis spectrum. Nevertheless we demonstrated that even though patients with BD+ had similar results to HC their minor symptoms assessed at the time of the examinations were correlated with neurophysiological functioning. Therefore it can be assumed that auditory screening processes might be disrupted also in BD+, not only in SZ, but the pathways leading to clinical symptoms are different. Further research is needed to provide more detailed data from wider scale of neuropsychological functioning of patients presenting with psychotic features.

'The original or primary cause of Madness is a mystery'

(William Pargeter, 1792)

1. INTRODUCTION

1.1. SCHIZOPHRENIA AND BIPOLAR AFFECTIVE DISORDER – CLINICAL ASPECTS

1.1.1. THE DEVELOPMENT OF TODAY'S DIAGNOSTIC CRITERIA FOR SCHIZOPHRENIA AND BIPOLAR AFFECTIVE DISORDER

Scientific research is slowly uncovering the mystery surrounding insanity. In the 19th century, medicine acquired more and more precise tools to investigate mental processes, which included psychophysiological and other experimental methods. In today's psychiatry practice, mental disorders with psychotic features represent one of the most challenging and burdening conditions for patients, health care practitioners and society.

Kraepelin was the first to differentiate manic-depressive psychosis and dementia praecox; the latter was renamed by Bleuler and is still known as schizophrenia (SZ). This name indicates that emotional and cognitive functions are split resulting in various dysfunctions. Disturbances of the affective system were also described early and their definitions have not changed profoundly during the last decades. Bipolar affective disorder (BD) includes mood changes between two poles; at these extremities psychotic symptoms might also occur. The Kraepelinian dichotomy still dominates the view of these two disorders despite their many similar characteristics.

In the first decades of scientific psychiatry, descriptive methods dominated the field of psychiatry, however, the need for unified nomenclature and diagnostic criteria emerged in the beginning of the 20th century. Diagnostic manuals were created to fulfil these needs – the International Classification of Diseases (ICD) was published in 1949 and the Diagnostic and the Statistical Manual of Mental Disorders (DSM) in 1952. The first few editions of diagnostic manuals reflected the Freudian approach of mental disorders and during their continuous development the current scientific results have been integrated into them. The

somewhat similar phenomenology of SZ and BD resulted in ongoing scientific debates about the aetiology and classification of these conditions.

1.1.2. SCHIZOPHRENIA AND BIPOLAR AFFECTIVE DISORDER IN DSM-5

The 5th edition of DSM has been published in 2013 (American Psychiatric Association). The definition of diagnostic criteria and differential diagnoses of mental disorders evoke fierce scientific debates. In the recent decade, the dimensional approach became stronger and evidences have accumulated in favour of it, questioning the validity of categorical diagnoses. Still, DSM-5 has kept the diagnostic categories; the dimensional approach was not able to convince the majority of the experts.

In the current DSM-5 the chapter entitled 'Schizophrenia Spectrum and Other Psychotic Disorders' includes the diagnoses delusional disorder, brief psychotic disorder, schizophreniform disorder, schizophrenia, schizoaffective disorder, substance/medication induced psychotic disorder, psychotic disorder due to another medical condition, catatonia, other specified schizophrenia spectrum and other psychotic disorder, and unspecified schizophrenia spectrum and psychotic disorder. The subtypes of schizophrenia are eliminated, as to address syndrome heterogeneity and subtyping would contradict the spectrum approach of diagnostics. The key features of a psychotic disorder are defined as the following: delusions, hallucinations, disorganized thinking and speech, disorganized or abnormal motor activity (catatonia included) and negative symptoms. The mental disorders belonging to this chapter are described in the order of severity as follows: delusional disorder, brief psychotic disorder, schizophreniform disorder, schizophrenia and schizoaffective disorder (Bhati, 2013).

The diagnosis of schizophrenia requires at least two psychotic symptoms to be present for 6 months with 1 month of active symptoms. These are stricter diagnostic criteria compared to those in the DSM-IV-TR. The inter-rater reliability measures of DSM-5 criteria in field trials were between 0.46 and 0.50, which is considered to be 'good'. Based on the data available, the DSM-5 is the most appropriate and reliable diagnostic handbook in the history of psychiatry (Bhati, 2013). Another important feature of DSM-5 is that its development has applied the most up-to-date scientific data and the opinion of wide expert audience.

Bipolar disorder in DSM-5 got an own chapter 'Bipolar and related disorders', where BD-I, BD-II and cyclothymia are to be found. BD-I is diagnosed if episodes of depression are alternating with manic phases; in BD-II hypomania is switching with depressive states. Some

diagnostic changes have been introduced, such as BD due to substance use or general medical condition were included. In the other specified and unspecified categories are conditions which do not meet the full criteria for the three classical forms of BD, either due to insufficient symptoms present or in the past, due to different time periods when the symptoms were obvious or due to insufficient information available. In BD, it is essential that the actual episode's polarity should be signified, although this is not always easy. Therefore, earlier a mixed episode could be diagnosed. In the DSM-5 only depressed or manic episodes can be coded with a mixed specifier, which might be attached to any manifestation of BD; as well as the specifier 'with anxious features'. The diagnostic criteria of a (hypo)manic episode are not only elevated mood but increased activity and energy are also needed to be present; and antidepressant-induced (hypo)manic symptoms are sufficient for a BD diagnosis if the symptoms persist after the cessation of the antidepressants (Severus & Bauer, 2014).

According to field studies, the reliability of BD-I diagnosis based on the new criteria is moderate (kappa: 0.56) and it is even lower for BD-II (kappa: 0.40). These numbers raise some concerns regarding the appropriateness of this diagnostic system, mainly due to the lack of inclusion of longitudinal variables (de Dios et al., 2014).

1.1.3. PSYCHOSIS SPECTRUM

Throughout the 20th century, research and clinical investigations have been aimed to create more and more specific and smaller diagnostic groups in order to provide the best understanding and treatment of each mental disorder. Diagnostic categories created walls between disorders, although many patients show overlapping symptoms and there is no strict evidence for biological distinction. A spectral or dimensional approach would be able to bridge this problem. This course resulted in the notion that mental disorders with psychotic features might constitute a psychosis spectrum and a dimensional diagnostic approach would be more appropriate. Symptom complexes – symptom dimensions, as psychosis show common biological roots and respond to the same pharmacological treatments. Placing patients into different symptom dimensions would be a more appropriate way to create clinical descriptions instead of clinical diagnostic categories. Some experts are on the opinion that BD should also be included in the psychosis spectrum, as many patients experience psychotic symptoms at some point of the illness progress (Ivleva et al., 2010).

Carpenter et al. (2009) evaluated evidence from genetic, imaging, electrophysiological, psychological and psychopathological studies regarding the common features of SZ and BD and they concluded that the overlap of the two conditions is not wide-ranging enough to consider them to be parts of one dimension.

The different diagnostic criteria are not present with the same severity by every patient; these might also be regarded as diagnostic dimensions in order to better illustrate the status of each person. A suggested dimensional model by van Os and Kapur (2009) is able to represent not only patients with SZ but with other mental disorders accompanied by psychotic features, too. The most common symptoms can be rendered into five categories or dimensions: positive symptoms, negative symptoms, cognitive symptoms, depressive symptoms and manic symptoms. In the development of psychotic disorders developmental and environmental factors play a key role besides genetic proneness (e.g. perinatal complications, social status, cannabis use, childhood traumas) and predispose to a special symptom pattern and age of onset. All the above taken together help to allocate each patient in the dimensional system depicted on Figure 1. This model provides a common framework for SZ and BD assuming that the two disorders have overlapping features.

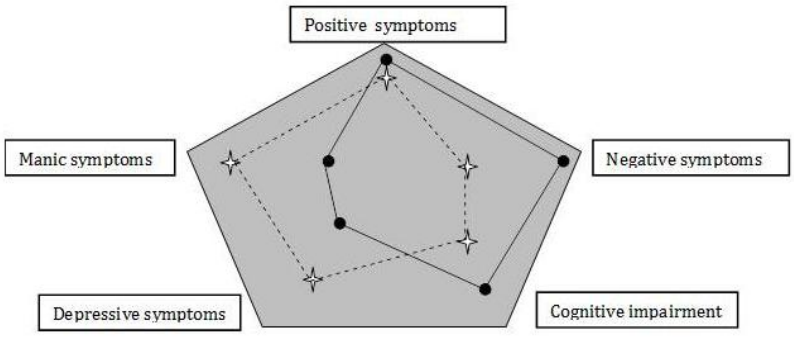

Figure 1. Possible representation of a patient with schizophrenia (black dots) and with bipolar affective disorder (white stars) in the five dimensions system proposed by van Os and Kapur (2009).

Craddock and Owen (2010) collected evidence supporting the common or overlapping aetiology and symptomatology of SZ and BD involving data from large-scale genetic studies. There is also accumulating evidence for the connection between SZ and autism spectrum, which might also indicate that SZ is also a neurodevelopmental disorder. Craddock and Owen propose a model for psychosis integrating dimensional and categorical approaches. According

to them the different DNA structural variants are expressed under the influence of various environmental factors and stochastic variations creating a unique phenotype. These can be categorized into different domains of psychopathology, which have dimensional nature. The mixture of symptom dimensions results in clinical syndromes, which constitute clinical diagnoses. Only the complex and multidisciplinary understanding of mental disorders might provide a clear picture of them, although there is a serious need for solid and distinctive biomarkers for early recognition of ultra-high risk (UHR) individuals. UHR and prodromal groups contain people who show early signs of a mental disorder which might be treated in order to prevent a full-blown psychosis.

1.1.4. THE ENDOPHENOTYPE CONCEPT IN THE VALIDATION OF PSYCHOSIS SPECTRUM

There are quite few studies comparing SZ and BD directly under the same circumstances. Consequently more research is needed for the clear differentiation of them and to obtain diagnostic biomarkers. Endophenotype (sometimes referred to as intermediate phenotype) research appears to be offering the appropriate biological methods for research and future diagnostics of psychotic disorders. Endophenotypes are heritable structural or functional characteristics of the brain related to specific illnesses that are theoretically bridging between genes and phenotypes and are independent from actual state of the patient (Gottesman & Gould, 2003). Smooth pursuit eye movements and event-related potentials (ERPs) are one of the most promising endophenotypes in SZ research. In recent years, studies also included BD patients but the results are still controversial (Ivleva et al., 2014). Figure 2 shows the framework of interactions among genes, endophenotypes and environmental factors in the development of psychiatric symptoms.

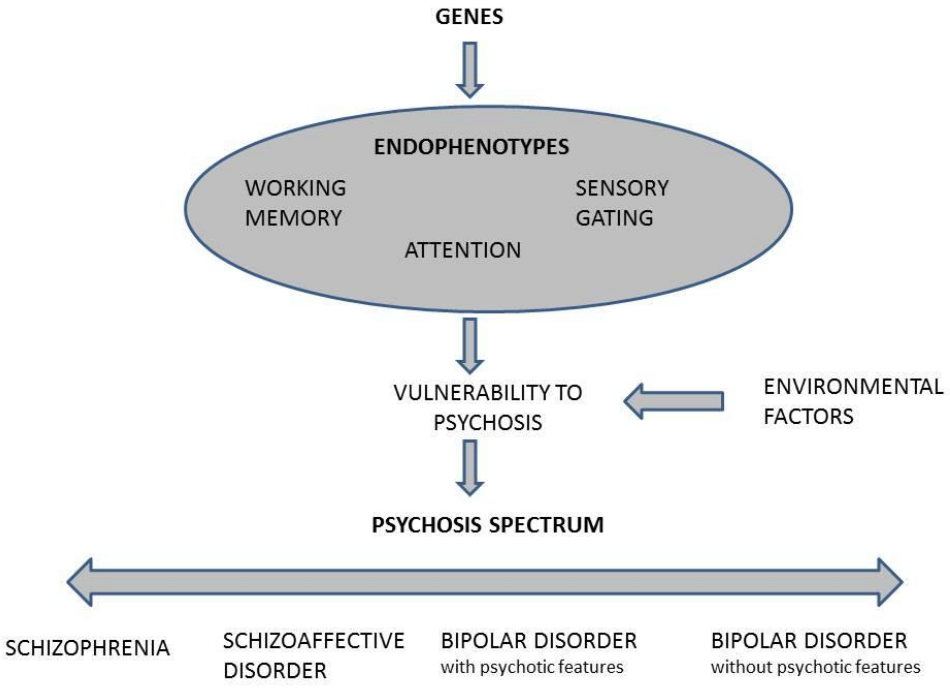

Figure 2. A simplified depiction of the possible involvement of candidate endophenotypes in the development of mental disorders constituting the psychosis spectrum.

The Bipolar and Schizophrenia Network for Intermediate Phenotypes (BSNIP) consortium was founded with the aim to generate wide ranging scientific data in order to identify biomarkers of clinical diagnoses with psychotic features. They used a standardized battery including clinical measurements, cognitive tests, electrophysiology, eye movement tracking, magnetic resonance imaging and genetic analyses. Despite the large sample size, comprehensive and standardized battery, the overlap of the data has proven to be too much and none of the candidate biomarkers were able to distinguish between patient groups or patients and heathy controls (HC) (Tamminga et al., 2014).

In this ongoing scientific debate the gathered data are in favour of the dimensional approach, but the centuries of old tradition needs even more evidence to be broken. At the end, the aim of psychiatric research is to find the biological basis for mental disorders and to be able to group and treat the patients accordingly; that is, to create an evidence-based psychiatry (Pearlson & Ford, 2014).

1.2. ERPs IN PSYCHOTIC DISORDERS – CANDIDATE ENDOPHENOTYPES

The main part of the present thesis focuses on ERPs in SZ and BD with anamnestic psychotic symptoms (BD+) patient groups. Clinical symptoms might be the result of dysfunctions in cognition and perception, which are processes of the nervous system. As it is hard to find the pathomechanisms of phenotypical characteristics based only on behavioural observations, it is logical to study the functions of the nervous system through imaging methods. The visual/structural resolution of electroencephalography (EEG) is not accurate enough to localize the source of an ERP, but the temporal accuracy is exquisite of this method. Every single stimulus has to be processed by the nervous system in order to make a decision of its importance, which can be traced by EEG. The electric change due to the neuronal activity can be observed on the EEG curve in the form of ERPs. ERPs emerge from the resting state EEG as positive or negative waveforms, which are usually named using their polarity and latency. The most studied ERPs in SZ are cortically produced beyond the temporal window of pure perceptual stimulus registration. In the following section I will introduce the most commonly studied auditory ERPs, as these have been included in our investigations (Figure 3 shows the ERPs included in Study I and their allocated functions).

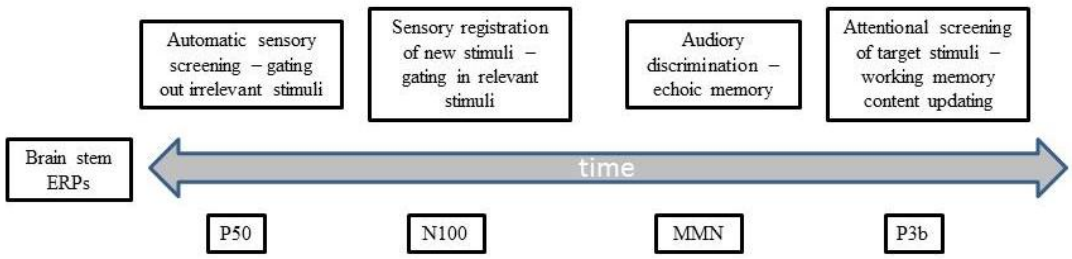

Figure 3. The auditory event-related potentials included in Study I and their allocated functions during the processing of auditory stimuli.

1.2.1. P50 IN PSYCHOTIC DISORDERS

P50 is a positive waveform occurring 40-75 ms after the stimulus onset; its amplitude is usually calculated from the previous negativity on the EEG recording. This ERP reflects the automatic sensory screening of new stimuli. If two identical sounds are close to each other in time (stimulus interval around 500 ms), the second generates a smaller P50. The most widespread paradigm to elicit P50 is a so called 'paired-click' design. The first sound is usually referred to as conditioning stimulus (S1) and the second is called test stimulus (S2).

The attenuated second P50 is the result of neuronal habituation or suppression of irrelevant stimulus reaction. The measurement of suppression can be quantified through the difference or the ratio of the amplitudes elicited by S1 and S2. The P50 ratio seems to be more reliable based on scientific data (Olincy, 2010).

The ability to suppress irrelevant stimuli makes it possible to focus our perceptional and cognitive capacity on the most adaptive way. The first step is to screen out stimuli automatically which are possibly unimportant at the present situation, for example because they are identical to a nearby (temporally or spatially) preceding stimulus. This basic sensory gating mechanism is reflected in P50 waveform diminishment to S2. The deficit of P50 suppression might occur via two different mechanisms and research is still ongoing regarding which is apparent in SZ. The first possibility is that the amplitude for S2 is similar in magnitude to the P50 for S1 indicating inhibitional dysfunction; the second option is that the sensory registration of new stimuli is damaged, that is the first P50 wave has smaller amplitude. Brenner et al. (2009) conducted a study focusing to this dilemma, and according to their results, the registration process showed deficits: the P50 waveform for S1 was diminished compared to HC. Others report the opposite result, the S2 sound elicits the same amplitude in the case of P50 and even N100 (Boutros et al., 2009; Sánchez-Morla et al., 2008). This controversy points out that further research is needed to clarify the nature of this dysfunction of sensory gating in SZ.

P50 suppression deficit is a well underpinned phenomenon in SZ (Olincy et al., 2010), but there are some studies reporting intact P50. It can be improved by atypical antipsychotic medication and nicotine consumption (Brockhaus-Dumke et al., 2008). Therefore it cannot be stated that the deficit of P50 suppression is a biomarker or an endophenotype in SZ or psychosis. Furthermore, better functioning level has been associated with less damaged P50 suppression; some studies showed a negative correlation between clinical symptom severity and sensory screening (Smith et al., 2013), but these results are not generally confirmed (Olincy et al., 2010; Devrim-Uçok et al., 2008). The P50 suppression deficit has also been described in BD with and without psychotic episodes and it appears to be independent from symptom severity (Sánchez-Morla et al., 2008; Carroll et al., 2008) and it is also compromised in unaffected relatives (Schulze et al., 2007). Scientific results tend to confirm P50 suppression deficit as a common feature in both SZ and BD (Cabranes et al., 2013). The degree of deficit in P50 suppression might differ by SZ and BD patients, as there are almost no studies to report similar results when directly comparing these groups. Based on P50 ratio

and frequency of leading saccades (indices of physiological inhibition), subjects can be rendered to their original clinical diagnosis with an accuracy of 90% (Martin et al., 2007).

1.2.2. N100 IN PSYCHOTIC DISORDERS

Usually studied in the same paradigm as the P50 the N100 reflects the registration of new auditory stimuli; this ERP is sensitive to the physical characteristics of sounds, not the contextual information (Turetsky et al., 2008). The N100 is generated in the auditory cortex and also shows habituation if two identical stimuli are heard within a short time window. It appears around 100 ms after the stimulus as a negative waveform on the EEG (Näätänen et al., 1978).

The N100 suppression is also an early sensory stimuli screening index and its deficit is a bit ambiguous in SZ and there are scarcely data regarding BD. The majority of results indicate that N100 suppression is impaired in SZ, but it is not clear when this deficit develops or whether it can be regarded as an endophenotype. The dysfunctional N100 gating can be observed after the first psychotic episode and it is not correlated with the symptom severity in SZ (Salisbury et al., 2010). Furthermore, the deficit appears in first degree relatives of SZ patients (Rosburg et al., 2008). In UHR groups, the N100 amplitude difference was significantly smaller in those who later developed psychotic symptoms. Furthermore the amplitude of N100 for S1 diminished in 3 years (van Tricht et al., 2015). A possible explanation for the ambiguous results of relatives might be that N100 deficits are only present in those with psychopathology, e.g. skizotypy (Turetsky et al., 2008). The N100 suppression deficit seems to be developing gradually and it peaks around the onset of the first psychotic episode of SZ. In BD disrupted N100 along with P50 gating deficit was reported in one study (Lijffijt et al., 2009).

1.2.3. MISMATCH NEGATIVITY IN PSYCHOTIC DISORDERS

The Mismatch Negativity (MMN) is regarded as the electrophysiological representation of auditory discrimination and echoic memory. MMN reflects the activity of the bilateral auditory cortex and the frontal lobe triggered by an irregular sound in a train of stimuli (Näätänen & Kähkönen, 2009). Oddball paradigms are usually applied to elicit this ERP where the subject is instructed not to pay attention (distractor task is given) to the sounds

played through headphones or speakers. The order of the stimuli is usually pseudo-random and contains standard sounds among which rare, different sounds occur. These deviant stimuli can differ from the standards in their frequency, duration, intensity or the stimulus interval. After the deviant stimulus a negativity emerges on the EEG with a latency of 100-250 ms, which has to be subtracted from the response registered to the standard sounds to get the MMN. Recently, this ERP is regarded as the reflection of the predicting processes consisting of automatic attentional and perceptual components; the MMN is generated in prefrontal and temporal cortical areas (Garrido et al., 2009). In other words, automatic change detection of the auditory cortex is manifested in the form of MMN. The amplitude and latency of this ERP depends on the nature of deviant stimuli, furthermore, the deficit of neural response in SZ to different deviant tones is not of the same magnitude. SZ patients are able to detect deviations from their prediction in their environment, but they fail to assess the magnitude of difference and the consequences of it. Therefore it is harder for them to detect salient and relevant stimuli – to update context which can be reflected in smaller MMN amplitudes (Todd et al., 2012).

Most studies investigate MMN elicited by pitch (pMMN) and duration (dMMN) deviant tones in SZ. The amplitude of pMMN decreases with the progression of SZ, which is not part of the normal ageing phenomena (Turetsky et al., 2008; Näätänen & Kähkönen, 2009). The dMMN is impaired even in UHR groups and first psychotic episodes (Näätänen & Kähkönen, 2009) with a continuing diminishment during the disorder course (Kiang et al., 2009); therefore this ERP is considered as the most robust endophenotype candidate in SZ (Jahshan et al., 2012). In BD+, studies report no significant differences compared to HC (Hall et al., 2007; Hall et al., 2009; Salisbury et al., 2007). It is unlikely that the dMMN deficit would be a general psychosis biomarker, although it could be used as a screening index for SZ in UHR groups.

1.2.4. P300 IN PSYCHOTIC DISORDERS

This ERP represents the conscious processing of unexpected rare target stimuli during a specific task. P300 can be decomposed into two positive waveforms; the P3a and the P3b are elicited in a short time range, which made them look like one ERP referred to as P300 (Polich et al., 2007). The P3a has a fronto-central maximum elicited by every unexpected stimulus, not only targets; it is registered after the processing of implicit context and is usually

considered as an orientating response. Actively screened target stimuli generate the P3b, which might represent the content updating of working memory based on the contextual information (Ford et al., 2010). The P3b usually has a parietal amplitude peak, but this can be slightly influenced by the modality of reaction given to the target stimuli; its latency is around 250-500 ms. The magnitude of the amplitude reflects the difficulty of the task, while the latency depends on the speed of information processing. It is proposed that these two ERPs are interrelated: P3a represents the frontal activity during attentional processes to screen out task-relevant stimuli. These cortical areas send a signal to temporal and parietal areas where P3b is generated reflecting memory functions (Polich et al., 2007).

Based on the literature P3a and P3b components of the P300 ERP reflect independent attentional processes, therefore their impairment in mental disorders shows different patterns. P3a is an index of automatic attentional orientation and it seems to be a stable deficit in SZ not influenced by illness duration or symptoms (Kiang et al., 2009). This deficit is regarded as one of the endophenotype candidates in SZ (Turetsky et al., 2015). The heritability of P3b deficit is questionable, as unaffected siblings do not differ from HC (Sumich et al., 2008). The deficit can be measured even in UHR groups and it is more pronounced by those who are to get treatment for psychotic symptoms in the near future (van Tricht et al., 2010). The P3a is also impaired before the onset of psychosis (Kaur et al., 2011) and the deficit intensifies after the first psychotic episode (Jahshan et al., 2012). In BD P3b amplitude is diminished and latency is prolonged (Ethridge et al., 2012), which is also measurable in unaffected relatives (Hall et al., 2007). In BD there are not enough data to draw any conclusions on how P3b might be involved in symptom development or if it fits the criteria for endophenotypes (Schulze et al., 2008). P3b amplitude deficit might be a psychosis endophenotype and not a specific biomarker, although symptoms might influence the characteristics of P3b (Chang et al., 2014; Merrin et al., 2006).

1.2.5. CORRELATIONS OF ERPS IN PSYCHOSIS

As mental disorders usually have a fluctuating course, state and trait characteristics can be differentiated among cognitive, emotional and neurophysiological deficits. To fully understand the symptoms observed in acute phases it is important to know how the nervous system's processes are altered in different disorders. With ERP studies the primary dysfunctions can be revealed and if measurements of clinical symptoms are also at hand the relationship of neuronal processes and observed alterations in functioning might be defined. Trait like dysfunctions can be the clues necessary to recognize those at risk for developing a mental disorder in time and might be the basis of prevention or early intervention.

The P50 suppression deficit correlates with the trait like severity of auditory hallucinations (AH; Smith et al., 2013) and both are generated in the temporal lobe. If sensory gating is dysfunctional, the environmental stimuli might flood the nervous system generating pathological associations and significances.

In SZ some studies found correlations between negative symptoms and N100 deficit (Boutros et al., 2009), some did not – not even longitudinally (Valkonen-Korhonen et al., 2012).

The impairment of MMN amplitude correlates with the volume deficit of Heschl's gyrus, which is located in the temporal superior gyrus and plays a role in the development of AH. Both functional and structural deficits are more pronounced with the progression of the disorder (Näätänen & Kähkönen, 2009). Rasser et al. (2011) found that dMMN and the volume of the right Heschl's gyrus are correlated, while the pMMN is related to the volumes of Heschl's gyri on both sides. Based on these data it could be assumed that MMN deficits, social functioning level and clinical symptom severity might be interrelated, but the results regarding this are still controversial (Rissling et al., 2012).

The P3b reflects selective attentional processes and the cognitive evaluation of stimuli, which might be correlated with some of the symptoms in SZ, e.g. avolition, attentional disorder and delusions (Turetsky et al., 2009). Without adequate attentional focus context updating becomes less appropriate and might lead to withdrawal and awkwardness in social situations burdening the patients. Ford et al. (2010) concluded that this might the main

pathogenic neuronal process in SZ. This theory has not been underpinned scientifically, as most studies found no correlation between P3b and symptom severity.

During speech production and perception in HC individuals the left fronto-temporal cortical region sends a signal in the form of an efference copy to the auditory cortex to inhibit responses elicited by external stimuli – this inhibition is referred to as corollary discharge. Presumably this inhibition is impaired in SZ and creates the experience of hearing voices or AH. This process can be investigated through the N100 measurements, as the amplitude of this ERP is smaller when hearing own voice. The explanation for this is that during speech production neural synchronisation precedes the pronunciation of words creating an efference copy and the inhibition can be observed in the suppression of N100. In SZ and BD+ the N100 suppression for own voice is not as strong as in HC groups, but the patients' healthy relatives did not differ from HC (Ford et al., 2013). This deficit is probably not a biomarker for psychosis, but it might be impaired due to the psychotic processes. The language perception reflected in N100 amplitude differs early in the SZ progress, although the dysfunction is not unambiguous in UHR groups (Perez et al., 2012). Although theoretically the development of auditory hallucinations might be due to N100 suppression deficit symptom severity and N100 amplitudes are not correlated (Ford et al., 2013; Perez et al., 2012). It can be concluded based on the comprehensive studies that predictive processes are dysfunctional in psychotic disorders due to the deficit of context updating (Ford & Mathalon, 2012). Another explanation for the generation of auditory hallucinations via sensory gating deficits is that SZ patients do not evaluate stimuli as important because there is a communication error between cortical areas and multisensory integration is also impaired. This results in disordered reality perception and diminished feeling of coherence, as patients are not able to track changes in external and internal context (Stekelenburg et al., 2013). The communication between relevant cortical areas can be hindered by the damaged arcuate fasciculus. The deficit of N100 suppression can be eliminated if there is a delay of 50 ms between the stimulus and the sound production; this also indicates the impaired corollary discharge function due to communication deficits (Whitford et al., 2011).

When we try to sum up the vast amount of data regarding early sensory processing in psychotic disorders it is obvious that it is clearly dysfunctional and affects cortical, cognitive functions too. The details and relationships are still vague and in the case of most ERPs the heritability of deficits is unsure. Sensory gating deficit – P50 – is a robust finding in SZ groups with familiar accumulation (Olincy et al., 2010); data involving other psychotic

disorders is not sufficient to draw conclusions. The registration of new and relevant stimuli reflected in N100 suppression deficit seems to be developing gradually with the progression of psychosis (van Tricht et al., 2015). Adequate and adaptive behaviour and reactions require continuous context updating of the auditory environment and inhibition of reactions to internally generated stimuli; these are also disrupted in SZ and can be measured through P3b and MMN (Todd et al., 2012).

There are only few studies which investigated more ERPs in the same sample, although this would be more informative than separate studies. There are some examples in SZ (Price et al., 2006; Turetsky et al., 2009; Gjini et al., 2010) and BD (Hall et al., 2009), even though their results are controversial. These discrepancies might be the result of differences in stimulus parameters, attention, arousal, smoking status or psychotropic medication (Patterson et al., 2008; Rosburg et al., 2008; Ivleva et al., 2010), which all affect the characteristics of ERPs. Studies reporting results of ERP paradigms from different patient groups usually assume that auditory ERPs represent consecutive stages of sensory processing. It is not factual though that these processes are interrelated, therefore ERPs might as well reflect distinct perceptional functions.

Turetsky et al. (2009) created factors from the different ERPs to clarify the perceptual processing differences of stimuli in HC and SZ groups. According to their results N100 and MMN are interrelated and their deficits contribute to alogia, formal thought disorder and language processing dysfunctions in SZ. Hall et al. (2012) created a big data pool and included among other physiologic measures P50, N100, P300 and MMN to investigate the neurophysiologic profiles of patients with SZ and BD. They created clusters based on the measurements, which did not overlap with the original diagnoses based on DSM-IV, so it supports the psychosis dimensional approach, as the two patient groups did not differ significantly from each other.

1.3. COGNITIVE CHARACTERISTICS OF PSYCHOTIC DISORDERS

1.3.1. GENERAL COGNITIVE DEFICIT AS A CORE FEATURE

Cognitive impairment contributes to the development and the outcome of SZ, but there is considerable less data about cognitive functioning in BD+. Cognitive dysfunctions can be detected in 40-80% of SZ patients; some of them precede the onset of the disorder and some remain even in remission (Heinrichs & Zakzanis, 1998; Kéri & Janka, 2001). In BD the data regarding cognitive deficits are contradictory and hard to replicate due to the heterogeneity of the samples (Ivleva et al., 2010; Chou et al., 2012; Green, 2006; Bourne et al., 2013). On a big sample using the same methodology both SZ and BD showed significant cognitive dysfunction compared to HC, although the performance of the patient groups did not differ except for the severity of malfunctioning. The latter could support the dimensional approach of psychosis (Tamminga et al., 2014; Reilly & Sweeney, 2014). Nevertheless, generalized cognitive impairment is present both in SZ and – to a lesser extent – in BD+ and leads to serious decrease in the quality of life.

Cognitive deficit might be observed on a general level – overarching every cognitive domain; and on specific cognitive areas. The different severity of dysfunctions could provide a special cognitive pattern characteristic for the different mental disorders. Identifying cognitive deficits specific for a mental disorder helps to differentiate the neurological processes underlying the pathomechanisms of the condition. Today most pharmaceutical treatments are not able to ameliorate the cognitive dysfunctions. Therefore it is of high importance to find therapeutic aims in this field through identifying the aetiology of them (Reilly & Sweeney, 2014). If there is no distinctive cognitive deficit in SZ or in BD that could indicate a common underlying neurophysiological dysfunction leading to cognitive dysfunctions. Unaffected relatives should also show signs of cognitive impairments in order to regard cognitive deficit as a psychosis biomarker or intermediate phenotype. Results so far are not supporting this notion either, as family members of SZ have discrete cognitive impairments, but BD relatives function at the same level as HC (Tamminga et al., 2014).

Cognitive functioning relies greatly on memory; proper encoding, storage and retrieval is essential to perform adequately on cognitive tasks. Human memory has been described with various models; the simplest distinction of its components is to use temporal definitions: short

and long term memory might be differentiated. Information stored in long term memory is processed by the working memory, which is a temporary storage. The most widespread model of working memory was developed by Baddeley; in his latest version 4 components were described: the central executive, the visuospatial sketchpad, the phonological loop and an episodic buffer. The central executive is controlling every working memory function, allocates attention and manipulates information. The phonological loop is a temporary storage for auditory information; the visuospatial sketchpad holds visual and spatial information necessary to complete the actual task. The episodic buffer is capable of encoding information from more modalities and it combines and integrates information (Repovs & Baddeley, 2006). According to functional imaging and cognitive neuropsychological results central executive functions can be linked to the dorsolateral prefrontal cortex (DLPFC), while working memory functions are mainly located in the prefrontal cortex (Collette & Van der Linden, 2002).

Executive functions not only refer to the work of the central executive; this term is used in a more wide meaning in cognitive neuropsychology. Executive functions are needed to organize one's behaviour, to create models of possible outcomes and of problem solving and to flexibly change non-efficient behaviours or schemas (Kopp, 2012). Executive functions are reflections of activity in the frontal lobes. As they interweave with every human action it is hard to give a simple definition, not to mention appropriate measurements. The complexity of executive functions resulted in many theoretical models; nevertheless there has been no perfect description. Based on the different theoretical frameworks many measurement methods have been developed and these neuropsychological tests are administered to asses cognitive functioning.

1.3.2. Wisconsin Card Sorting Task

There is a wide variety of neuropsychological tests measuring different cognitive functions with variable accuracy and it is hard to pick one most suitable and informative for scientific research. The Wisconsin Card Sorting Task (WCST; Heaton, 1981) is widely used for the measurement of working memory functions and shifting ability (Polgár et al., 2010). Impairments of the dorsolateral-prefrontal cortex are well reflected in the alterations of WCST performance (Heaton et al., 1993; Kéri et al., 2001). Although executive functions are more likely the reflections of neural activity involving cortical and subcortical areas. WCST performance might be disrupted by the dysfunction of more cortical areas, only set-shifting

can be bound to prefrontal areas (Nyhus & Barceló, 2009). Based on robust research data shifting function measured by WCST is disrupted in SZ, while in BD results are ambiguous (Green, 2006; Bourne et al., 2013). When measurable deficit is present in BD it is independent from illness duration and symptom severity, but correlates with psychosocial functioning, which is an important outcome index (Strejilevich & Martino, 2013). The WCST is a good tool for measuring cognitive impairment being most likely a core feature in psychotic disorders like SZ and BD.

1.4. CORRELATIONS OF COGNITIVE DEFICITS AND ERPS IN PSYCHOTIC DISORDERS

If we consider that cognition is the result of neural system processes and ERPs are reflections of the brain's activation it can be assumed that the performance on neurocognitive tests and ERPs are correlated. In cognitive functioning it is of essential importance that new stimuli are noticed in order to decide whether they are relevant in the actual context. N100 reflects the registration process building the basis for working memory manipulations. Few studies investigated neuropsychological profiles and ERPs; one example is Boutros et al. (2009). This paper reports strong correlation between the different measures of WCST and N100 suppression deficit in SZ; both deficits might indicate frontal lobe dysfunction. Increased PE% and P3b amplitude reduction was found in SZ (Merrin et al., 2006). Task-set shift initiating clues elicited a P3a – orientation, attention allocation; feed-back clues generated a P3b waveform with increasing size parallel with memory load increment – updating processes (Barceló et al., 2002); task-set shift in WCST appears to elicit a P300 waveform reflecting working memory processes (Mestrović et al., 2012). Cognitive dysfunction measured with different neurocognitive tests correlates with the characteristics of the P300 waveform (Chang et al., 2014) and dMMN amplitude (Toyomaki et al., 2008).

Cognitive dysfunctions and dMMN deficit are measurable and correlated after the first psychotic episode not only in SZ but even in affective spectrum patients (Kaur et al., 2011). Cortical processes might compensate for the deficits of automatic dysfunctions. When subjects are instructed to pay attention to the sounds during an oddball paradigm or even to push buttons when hearing the rare tones the MMN deficit decreases in SZ (Rissling et al., 2013).

Many factors need to be clarified regarding auditory ERPs and their relations to clinical symptoms and cognitive functioning is psychoses. Deficits in UHR groups or after the first episode of psychosis may help screening and early intervention and could even shed light on the genetic background of SZ and BD. The processes through which early neurobiological dysfunctions manifest as cognitive deficits or clinical symptoms might provide pharmacological and therapeutic targets.

2. AIMS

Study I aimed to involve 5 ERPs in one session under the same circumstances to reveal similarities between SZ and BD+ groups' auditory processing. Furthermore this experimental design aimed to shed light on the relationship among these ERPs through comparing P50 and N100 suppression, pMMN, dMMN, and P3b in SZ, BD+ and in HC. We included both pMMN and dMMN as research data suggest that they reflect at least partially different neural processes and the reported deficits in psychotic disorders are also distinct. There is a significant phenomenological overlap between SZ and BD+ therefore we assumed that the deficits will show a similar pattern in the two patient groups. The trait or state like nature of ERP deficits might be determined through correlational analyses with clinical symptom severity. It was expected that P50 suppression and P3b parameters would be abnormal both in SZ and BD+. Furthermore we proposed that measures of N100 suppression and MMN (primarily dMMN) would be impaired mainly in SZ.

The focus of Study II was the relationship between cognitive functioning in SZ and BD+ and clinical symptom severity. Based on literature data both in SZ and BD+ general cognitive deficit represents a core feature and affects prognosis. Results are still controversial regarding the relationship of cognitive functioning and clinical symptom severity. It was assumed that patients with SZ will have more severe cognitive deficits measured with WCST than BD+ group, while BD+ might be slightly impaired.

Sensory processing and attentional orientation influence the efficacy of cognition, especially of working memory. P3b is a reflection of working memory operations and WCST is believed to measure the result of these processes. By HC subjects during the administration of WCST P3b waveforms can be recorded when a set shift is due (Mestrović et al., 2012). Therefore we assumed that the characteristics of P3b will correlate with the performance on WCST in all three groups.

As the samples of the two studies were almost identical, correlations of ERP measures and WCST indices were also analysed. We presumed that the amplitudes of P3b and MMNs would be positively correlated with the measures of the WCST, as it requires focused attention and continuous change detection.

The data presented here aimed to overcome methodological and patient heterogeneity; therefore the procedures were applied under the same circumstances on both disorders and only BD+ patients were included.

3. METHODS

3.1. STUDY I

3.1.1. PARTICIPANTS

Twenty BD+, N=20 SZ patients and N=21 HC subjects were enrolled. All patients were outpatients, under medication and in a clinically stable mental state (Table 1). The diagnoses matched both ICD-10 and DSM-IV-TR criteria and were set by a psychiatrist. The patients had no other Axis I diagnoses, while control subjects had no Axis I and II psychiatric history. All subject had a negative history for drug/alcohol dependence according to DSM-IV-TR criteria, head trauma with loss of consciousness and neurological disorders. Moreover, none of our participants reported alcohol or drug abuse (as defined by DSM-IV-TR) within the past 12 months. Former alcohol abuse occurred in half of our sample, whereas the number of former marijuana abusers was very small (N=3 HC, N=0 SZ and N=3 BD+ participants). Smoking status was obtained by self-reporting the number of cigarettes smoked per day. Audiometry was used to screen for hearing impairment and none of the subjects demonstrated a substantial threshold elevation (greater than 20 dB at 1000 Hz and 1500 Hz). All subjects signed the informed consent prior to the recording session. The protocol was approved by the Ethics Committee of the University of Szeged.

3.1.2. CLINICAL SYMPTOM RATING SCALES

The interviews for the Positive and Negative Symptoms Scale (PANSS; Kay et al., 1987), Young Mania Rating Scale (YMRS; Young et al., 1978) and Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979) were conducted at the time of examination.

3.1.3. PROCEDURE OF ERP RECORDING

The recordings were performed in a sound-proof, electrically shielded room. The participants sat in a comfortable armchair. The five electrophysiological indices were recorded in a 45 minute-long session. Given that all patients were in a clinically stable mental condition, there were no cooperation problems during the recordings. The three paradigms were conducted in the following order: P50 and N100 suppression paradigm, MMN session

and the active oddball task to elicit the P3b. This order was chosen to establish a gradually increasing complexity of stimulus sequences and to minimize attentional effects in the first two sessions. The sounds were delivered through headphones, and since every subject had normal hearing the sound intensity was the same for all participants.

For studying P50 and N100 suppression we used a 'paired-click' paradigm with 70 pairs of clicks (S1 and S2; all 110 dB SPL, 0.1 ms) that were separated by 500 ms. The interval between the click pairs varied randomly between 10 and 15 seconds.

The MMN paradigm consisted of 900 standard (1000 Hz, 80 dB SPL, 100 ms), 50 pitch deviant (1500 Hz) and 50 duration deviant (250 ms) sinusoidal tones (10 ms rise/fall times) that were presented in a fixed, 9 standard/1 pitch deviant/9 standard/1 duration deviant order (Näätänen et al., 2004) with a stimulus-onset asynchrony (SOA) of 1 second. The participants read a daily newspaper during the recording.

In the P3b paradigm, 60 target sinusoidal tones (1500 Hz, 80 dB SPL, 100 ms) appeared randomly among 240 standard (1000 Hz) tones with a SOA of 1 second, and our subjects were asked to count the target ones silently. The recording was considered successful only if the error percentage was below 10%. One BD patient did not count correctly, so her data was excluded from the P3b analysis.

3.1.4. EEG RECORDING AND ANALYSIS

Recordings were done with a Nicolet Bravo Multimodality System (EMS Co, Korneuburg, Austria). The EEG sampling frequency was 1024 Hz, the analogue filter was set to 0.1–100 Hz. Nineteen tin scalp electrodes (Fp1, Fp2, F3, F4, F7, F8, Fz, C3, C4, Cz, T3, T4, T5, T6, P3, P4, Pz, O1, O2) mounted in an elastic cap (ElectroCap International, Eaton, USA) were placed in accordance with the international 10/20 system (Jasper, 1958). Additional two electrodes were placed above and below the left eye for recording vertical eye movements. The reference electrode was the left earlobe during recording and all data were re-referenced to linked earlobes offline. Electrode Fpz served as ground. The impedance was kept <10 kOhm. The data were analysed with the BrainVision Analyzer software (Brainproducts GmbH, Munich, Germany).

Continuous EEG data were segmented with epoch lengths from 100 ms pre-stimulus to 600 ms post-stimulus. After baseline correction (from -100 to 0 ms), an ocular artifact removal algorithm was performed (Gratton et al., 1983). Artifact rejection was conducted automatically (amplitude criterion: ±100 μV), but epochs were visually also inspected for

muscle and horizontal eye movement-related artifacts. The number of rejected epochs for each ERP was below 20% and univariate ANOVAs performed separately for all ERPs revealed no differences among participant groups ($p>0.29$) regarding rejection ratios. For each paradigm, different high- and low-pass filters (phase shift-free Butterworth filters, 24 dB/octave for all) were applied. In line with the recommendation of a recent meta-analysis, our P50 data were analysed with both 3 Hz and 10 Hz high-pass filters with a constant 100 Hz low-pass filter setting (Patterson et al., 2008). For N100 analysis, a 0.1-20 Hz filter setting was used to enable comparison with earlier studies (e.g. Lijffijt et al., 2009). The same filter was used for MMN analysis (Duncan et al., 2009), while a slightly higher low-pass filter (30 Hz) was applied to our P3b data. This was done to eliminate higher frequencies and to enable reliable peak detection although generally a low-pass filter of 100 Hz is recommended for the analysis of P3b data (Duncan et al., 2009). After averaging, ERP amplitude and latency parameters were measured manually. In the case of one male BD+ patient, MMN data could not be analysed due to transitory hardware problems.

For defining the P50 wave, the P30 peak was identified first at electrode Cz (Patterson et al., 2008). The P50 peak-to-peak amplitude was measured between the P50 peak in the 30-70 ms latency interval and the preceding trough. In the case of the P50 obtained for S2, its latency had to be within 10 ms to that obtained for S1. The maximum negativity between 80 and 120 ms at electrode Cz was considered as the N100 and the preceding positive trough served as comparison point from which the peak-to-peak amplitude was measured. To determine the degree of P50 and N100 suppression, we calculated both ratio (S2/S1) and difference (S1-S2) values.

For MMN analysis, difference waveforms (deviant-standard) were computed. Amplitude relative to pre-stimulus baseline and peak latency parameters of the pMMN and dMMN were measured as the most negative peaks between 140-250 ms and 200-300 ms post-stimulus respectively. Since the MMN typically shows frontocentral maxima, peak amplitude and latency parameters were measured at electrodes Fz, F3, F4, Cz, C3 and C4.

The P3b was assessed at electrodes Fz, F3, F4, Cz, C3, C4, Pz, P3 and P4 as the largest positivity between 300-500 ms for potentials obtained for the target tones. Amplitude relative to pre-stimulus baseline and peak latency parameters were measured.

3.1.5. STATISTICAL ANALYSIS

Data were analysed with SPSS version 20 (Statistical Package for Social Sciences, Armonk, NY: IBM Corp.). The level of significance was set at 0.05 by each statistical probe. Distributions of gender and smoking status (smokers vs. non-smokers, number of cigarettes per day) were compared between groups by chi-square test, while age and years of education were compared with Mann-Whitney U test. For all five ERPs a repeated-measures analysis of covariance (ANCOVA) as a primary analysis was applied separately for amplitude and latency measures. ERP parameters were entered as dependent variables, with stimulus order (S1 and S2 for P50 and N100 suppressions), electrode positions (frontal-central for pMMN and dMMN, frontal-central-parietal for P3b; left-midline-right for pMMN, dMMN and P3b) as within-subject factors, group as between subject factor and smoking as covariate. Smoking status was included because alpha 7 nicotinic receptors have been associated with information processing abnormalities in SZ, especially regarding P50 suppression (Leonard et al., 2002). To further investigate differences in interaction effects among groups, exploratory pairwise group comparisons were performed with follow-up repeated-measures ANCOVAs. One-way ANCOVAs with Bonferroni post hoc tests were performed to assess group differences in P50 and N100 S1 and S2 amplitudes, ratio and difference values. Pearson correlation was applied to reveal any relationships among ERP measures and clinical symptom severity.

3.2. STUDY II

3.2.1. PARTICIPANTS

Outpatients from the Psychiatry Clinic in Szeged were involved who have been diagnosed with SZ (N=26) and BD+ (N=24) according to the diagnostic criteria of the DSM-IV-TR. Less than 10% of the patients asked to participate refused to do so. Their data were compared to those of N=21 HC; this group was screened for psychiatric disorders. Out of 31 volunteers 10 proved to suffer from some kind of psychiatric disorder; this was in four cases major depression, furthermore 1 dysthymia, 1 BD-II, 4 past suicide attempts, 3 phobic disorder, 1 alcohol dependency and 5 personality disorders were revealed, in 5 cases there were comorbid disorders, thus they were excluded from the study. After obtaining written informed consent the neurocognitive tests were administered. The study design was approved

by the Ethics Committee of the University of Szeged. The investigators were not blind regarding the clinical diagnoses of the participants.

In the final analysis the data of 71 people (females=32, males=39; HC=21, SZ=26, BD+=24) were included with an age range from 20 to 59 years (mean=37.68, SD=10.24). Years spent in education varied between 8 and 20 years (mean=12.45, SD=2.37); their IQ measured by WAIS-III scored from 89 to 135 (mean=111.58, SD=10.78). There were no significant differences in the demographic data of the three groups; although the BD+ group's mean age was slightly higher than the other two groups' (see Table 3).

3.2.2. CLINICAL SYMPTOM RATING SCALES

The HC group was screened for psychiatric disorders by a trained psychiatrist and a psychologist through the Mini International Neuropsychiatric Interview 4.4 (MINI; Balázs et al., 1998) and the Structured Clinical Interview for DSM-IV Axis II (SCID-II; First et al., 1997). Both patient groups were administered the PANSS. Furthermore the BD+ patients also underwent a rating through the YMRS and the MADRS. For the mean scores of clinical scales see Table 4.

3.2.3. WCST

WCST is widely used for testing frontal lobe functions and its validity has been proven by many imaging studies. This neuropsychological test has many functional dimensions, e.g. it measures the flexibility of thinking and learning, conceptualization, shifting, perseveration and response inhibition.

In this study the manual (paper-pencil) version of WCST was used. It consists of 128 cards patterned with four different colours and shapes. Four stimulus cards are put in front of the subject who has to order the top card from the deck to one of the stimulus cards according to a rule he/she thinks is valid. The investigator only gives feedback on whether the choice was right or wrong and the subject has to deduct from this feedback the right rule. There is always only one aspect determining the rule (colour, number or form). Without previous warning after ten right choices the investigator changes the rule which has to be noticed based on the feedback. The subject should shift the ordering strategy. The task ends after six rule

changes (colour, form, number, colour, form, number) or if all the cards are paired. It can be finished faster if the subject notices the change and shifts his choice pattern as soon as possible. In the case of good frontal functioning there are few choices based on invalid rules. Many measures can be calculated from this task; in the present study we used four of them: completed categories (CC, maximum score: 6), perseverative error percentage (PE%), failure to maintain set (FMS), conceptual level response percentage (CLR%). Mean scores of the three groups are presented in Table 4.

3.2.4. Statistical analysis

Data were analysed with SPSS version 20. The level of significance was set at 0.05 by each statistical probe. Shapiro-Wilk test was applied to examine the normal distribution of the data besides graphic evaluation. The demographic variables of the groups were compared through one-way ANOVA, chi-square, Kruskal-Wallis and paired Mann-Whitney probes. Clinical scales and cognitive measures were analysed with Kruskal-Wallis and paired Mann-Whitney tests; their relationships were examined through Spearman's rank correlations.

3.3. Relationship of ERPs and WCST

The samples analysed in Study I and II were partially overlapping. The correlational analysis of ERP measures and WCST scores was calculated from the data of N=9 HC, N=17 SZ and N=20 BD+ subjects by the means of Pearson's correlation. Due to the small sample size results of HC should be treated with caution.

4. RESULTS

4.1. STUDY I

4.1.1. DEMOGRAPHIC VARIABLES, CLINICAL SCALES

Regarding the demographic characteristics (Table 1) the groups differed only in years spent in school (HC-SZ: Z=-2.45; p=0.016; BD+ vs. SZ: Z=-2.58; p=0.01). PANSS scores in the SZ group were significantly higher than in BD+ (PANSS-P: Z=-2.64; p=0.008; PANSS-N: Z=-3.03; p=0.002; PANSS-T: Z=-2.44; p=0.015). While mean YMRS values were extremely low in BD+ patients, the mean MADRS scores were indicative of mild depressive symptoms. A more careful look at the data revealed that 11 BD+ patients were completely euthymic (MADRS < 7), 5 BD+ patients showed mild depressive symptoms (MADRS 7-19) and 4 BD+ patients presented with moderate depressive symptoms (MADRS 20-34).

Table 1. Demographic and clinical characteristics of the groups included in Study I

	Groups					
	Controls (N=21)		Patients with SZ (N=20)		Patients with BD+ (N=20)	
	Mean	(±SD)	Mean	(±SD)	Mean	(±SD)
Age	37.33	(±8.76)	39.8	(±9.64)	42.9	(±9.6)
Years of education	13.24	(±2.3)	11.16$^{*\#}$	(±2.22)	13.75	(±2.88)
Illness duration			13.44	(±8.97)	14.44	(±9.21)
PANSS positive			11.78$^{\#}$	(±4.45)	8.6$^{\#}$	(±1.79)
PANSS negative			16.33$^{\#}$	(±6.35)	10.5$^{\#}$	(±3.85)
PANSS global			30.39	(±11)	25.25	(±6.9)
PANSS total			58.50$^{\#}$	(±19.94)	44.35$^{\#}$	(±11.52)
	N		N		N	
Gender (male/female)	11/10		10/10		11/9	
Smokers	11		8		11	
Typical antipsychotics	-		3		0	
Atypical antipsychotics	-		19		8	
Mood stabilizers	-		2		19	
Antidepressants	-		5		9	
Benzodiazepines	-		13		6	

Note: The * symbol indicates significant (p<0.05) difference compared to HC, whereas $^{\#}$ marks significant (p<0.05) difference compared to the other patient group.

4.1.2. ERP DATA

The mean and standard deviation (SD) values of all ERPs are shown in Table 2. The interaction with smoking status was not significant in either of the analyses performed. As expected, we found a significant effect of stimulus order (i.e. smaller S2 than S1 amplitudes) for P50 suppression (3 Hz low-pass: $F_{1,54}$=11.867; p=0.001; 10 Hz low-pass: $F_{1,54}$=27.777; p<0.001; Figure 4), but neither the effect of group, nor stimulus order x group interaction was significant. S1 and S2 amplitude, P50 gating ratio and difference values were not significantly different either, regardless of the low-pass filter setting. For N100 suppression (Figure 4) significant effects of stimulus order ($F_{1,54}$=57.044; p<0.001), whereas we found an almost significant interaction between stimulus order and group ($F_{2,53}$=3.104; p=0.053). Follow-up pairwise comparisons revealed that this interaction was due to a significantly poorer suppression in SZ than HC (stimulus order x group interactions: $F_{1,37}$=5.997; p=0.019). Although the analysis of the N100 difference values revealed a non-significant group main effect ($F_{2,53}$=3.104; p=0.053), Bonferroni corrected post hoc comparisons indicated a weak, but statistically significant difference between SZ and HC values (p=0.048). Neither N100 ratios nor S1 and S2 amplitude values did differ between the three groups.

The MMN waveforms are presented in Figure 5. While pMMN amplitudes were comparable across groups, we found a significant group effect for pMMN latency ($F_{2,53}$=10.046; p<0.001). The pairwise comparisons revealed that this was due to longer pMMN latencies in BD+ than in HC ($F_{1,36}$=18.36; p<0.001) and SZ ($F_{1,34}$=15.131; p<0.001). Although the effect of group for dMMN amplitudes was not significant ($F_{2,53}$=2.807; p<0.069), the comparison of the HC and SZ data revealed a significant difference ($F_{1,36}$=6.281; p=0.017) with smaller amplitudes in SZ (Table 2). This difference was not affected by scalp topography. Despite the relatively small dMMN mean amplitude in the BD+ group (Figure 4 and Table 4), the HC vs. BD+ comparison was not significant ($F_{1,36}$=3.658; p<0.067). For dMMN latency, we found a significant group effect ($F_{2,53}$=3.737; p=0.03), which was secondary to shorter latencies in SZ when compared to HC ($F_{1,36}$=4.349; p=0.044) and BD+ ($F_{1,34}$=9.364; p=0.004).

No significant differences between the groups were found regarding accuracy rates of target tone counting in the P3b paradigm (HC: 98.55%±2.39%; SZ: 99.44%±1.66%; 97.97%±3.48%; F=0.8; p=0.45). In the case of the P3b amplitude (Figure 6) the analysis revealed a significant group effect ($F_{2,53}$=3.826; p=0.028), which was secondary to smaller

amplitudes in SZ when compared to controls ($F_{1,36}$=6.441; p=0.016) and patients with BD+ ($F_{1,34}$=7.334; p=0.011). This amplitude reduction in SZ was not influenced by scalp topography. For P3b latency values, no group differences were found.

Table 2. ERP measures of the groups included in Study I

	Groups		
	Controls (N=21)	Patients with SZ (N=20)	Patients with BD+ (N=20)
Amplitudes (μV), latencies (ms) and gating ratios (%)	Mean (±SD)	Mean (±SD)	Mean (±SD)
P50 S1 amplitude at Cz	3.64 (±2.83)	3.29 (±3.79)	2.66 (±1.94)
P50 S2 amplitude at Cz	1.93 (±1.73)	1.93 (±2.14)	1.24 (±0.87)
P50 amplitude difference	1.72 (±1.99)	1.36 (±2.59)	1.28 (±2.07)
P50 ratio	0.72 (±0.64)	0.75 (±0.71)	1.2 (±2.56)
N100 S1 amplitude at Cz	-10.13 (±6.17)	-4.73 (±3.26)	-8.08 (±6.87)
N100 S2 amplitude at Cz	-3.76 (±2.65)	-2.09 (±2.74)	-3.84 (±2.69)
N100 difference	-6.38 (±5.16)	-2.63* (±3.81)	-4.24 (±5.35)
N100 ratio	0.58 (±0.84)	0.42 (±0.84)	0.49 (±0.63)
dMMN amplitude at Cz	6.94 (±3.04)	4.74* (±2.44)	4.1 (±4.12)
dMMN latency at Cz	246.93 (±31.82)	225.49*# (±22.48)	245.73 (±26.29)
pMMN amplitude at Cz	4.41 (±2.96)	4.11 (±2.86)	4.09 (±3.28)
pMMN latency at Cz	163.88 (±18.5)	157.67 (±25.97)	186.99*# (±18.95)
P3b amplitude at Pz	9.26 (±6.49)	4.87*# (±2.74)	9.9 (±7.11)
P3b latency at Pz	380.86 (±26.72)	374.9 (±24.97)	386.1 (±20.99)

Note: The * symbol indicates significant (p<0.05) difference compared to HC, whereas # marks significant (p<0.05) difference compared to the other patient group.

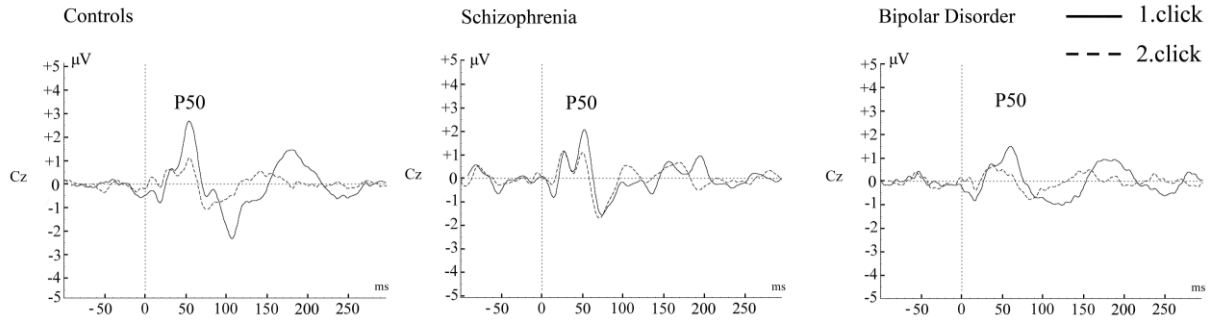

Figure 4. Suppression of the P50 ERP at electrode Cz in the three groups (data filtered with 10 Hz high-pass and 100 Hz low-pass filters).

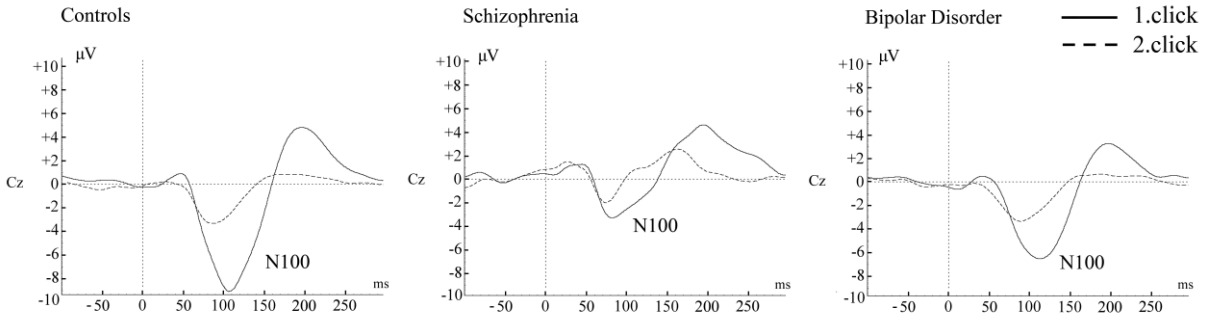

Figure 5. Suppression of the N100 component at electrode Cz in the three groups.

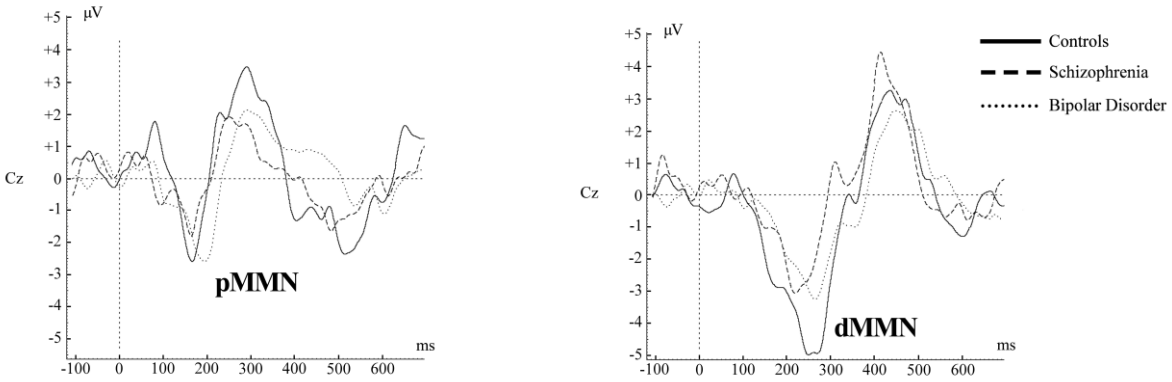

Figure 6. Changes in MMN across the three groups for pitch and duration deviant sounds at electrode Cz.

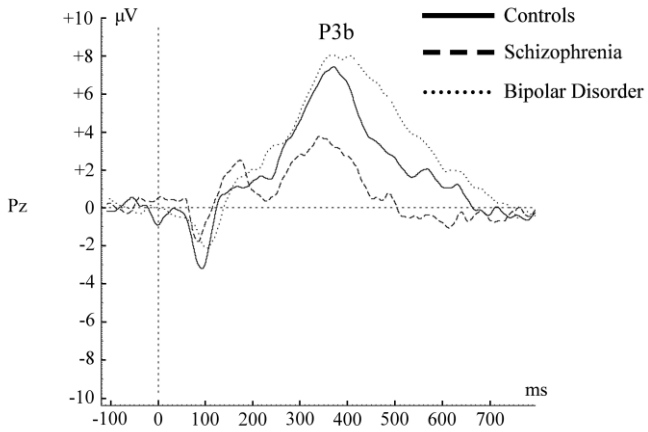

Figure 7. Changes in the P3b component obtained for the target tones at electrode Pz in the three groups.

4.1.3. CORRELATIONS OF ERPS AND CLINICAL SCALES

In the SZ group only the latency of P3b and the positive scale of PANSS were correlated (r=0.469, *p*=0.05). By BD+ patients P3b latency was correlated with both positive (r=0.558, *p*=0.02) and negative (r=0.520, *p*=0.032) scores of PANSS, while P3b amplitude had only paralleled with the positive symptom severity (r=-0.506, *p*=0.038). In the BD+ group P50 gating measures had several correlations with the PANSS subscales: positive symptoms with P50 amplitude for S1 (r=-0.582, *p*=0.014), P50 ratio (r=0.579, *p*=0.015) and P50 difference (r=-0.509, *p*=0.037); general scale with P50 ratio (r=0.540, *p*=0.025); total score with P50 amplitude for S1 (r=-0.482, *p*=0.05) and P50 ratio (r=0.521, *p*=0.025). The YMRS scores of patients with BD+ were correlated negatively with P50 ratio (r=0.560, *p*=0.013).

4.2. STUDY II

4.2.1. DEMOGRAPHIC VARIABLES, CLINICAL SCALES

There were no significant differences among SZ, BD+ and HC groups in the involved socio-demographic values. In patients with BD+ there was a positive correlation between years spent in education and the severity of general symptoms (r=0.42, *p*=0.022) and IQ scores negatively correlated with severity of positive symptoms (r=-0.44, *p*=0.017). Age of HC negatively correlated with WCST's CLR% (r=-0.37, *p*=0.049) and CC (r=-0.44, *p*=0.023). The age of SZ group had a negative correlation with CC (r=-0.37, *p*=0.03) and

FMS (r=-0.38, *p*=0.028). Age and MADRS score were negatively correlated in BD+ group (r=-0.47, *p*=0.012) and a negative relationship was revealed with PANSS general score (r=-0.46, *p*=0.012) and total score (r=-0.43, *p*=0.019). The age of BD+ patients correlated negatively with PE% (r=0.35, p=0.047). PANSS and WCST scores had no correlations in the SZ group.

In the BD+ group MADRS and YMRS scores were analysed regarding their relationship with demographic variables and WCST scores. YMRS scores had a positive correlation with the positive subscale of PANSS (r=0.61, *p*=0.001). MADRS scores were higher in better educated patients (r=0.54, *p*=0.004). MADRS scores were negatively correlated with age (r=-0.47, *p*=0.012) and PE% (r=-0.36, *p*=0.047).

PANSS scores of the two patient groups differed significantly only in the negative and total subscales, the SZ group showed more severe symptoms (see Table 3).

Table 3. Sample characteristics of SZ, BD+ and HC groups included in Study II

	Groups							
	Controls (N=21)		Patients with SZ (N=26)		Patients with BD+ (N=24)			
	Mean	(±SD)	Mean	(±SD)	Mean	(±SD)	F	*p*
Age (years)	35.33	(±10.06)	35.81	(±10.4)	41.75	(±9.35)	3.05	0.054
IQ	112.33	(±10.71)	109.35	(±11.49)	113.13	(±10.19)	0.78	0.46
							χ^2	*p*
Education (years)	12.57	(±2.4)	11.5	(±2.05)	13.38	(±2.36)	4.96	0.08
Gender	N	(%)	N	(%)	N	(%)	0.6	0.74
Males	10	(47.6%)	13	(50%)	16	(66.7%)		
Females	11	(52.4%)	13	(50%)	8	(33.3%)		
			Mean	(±SD)	Mean	(±SD)	Z	*p*
Age at onset (years)			25.62	(±6.09)	31.22	(±10.41)	-1.7	0.09

4.2.2. WCST

Performance on the WCST was significantly different when comparing SZ, BD+ and HC groups (see Table 4). PE% (Z=-2.76, *p*=0.006) was higher in the SZ group, CLR% (Z=-3.05, *p*=0.002) and CC (Z=-3.46, *p*=0.001) were lower in patients with SZ when compared to HC. Performance was poorer in SZ measured by CLR% (Z=-2.12, *p*=0.034) and CC (Z=-2,

p=0.045) compared to BD+. BD+ and HC groups showed no difference on either measure of WCST.

Table 4. Clinical and WCST measures of the groups included in Study II

	Groups							
	Controls (N=21)		Patients with SZ (N=26)		Patients with BD+ (N=24)			
	Mean	(±SD)	Mean	(±SD)	Mean	(±SD)	Z	*p*
PANNS								
Positive			10.48	(±4.1)	8.38	(±1.31)	-1.44	0.15
Negative			15.6$^{\#}$	(±6.42)	10.38	(±3.92)	-3.27	<0.001
General			28.88	(±10.42)	23.75	(±6.05)	-1.69	0.09
Total			54.48$^{\#}$	(±19.31)	42.5	(±9.95)	-2.38	0.02
YMRS					1.43	(±1.78)		
MADRS					8.26	(±10.73)		
WCST							χ^2	*p*
PE%	13.62	(±9.76)	24.65*	(±18.3)	17.21	(±10.96)	6.82	0.03
CLR%	69.33	(±21.96)	45.15$^{*\#}$	(±25.44)	60.58	(±26.68)	9.59	0.01
CC	5.24	(±1.58)	3.15$^{*\#}$	(±2.15)	4.33	(±1.99)	13.02	0.001
FMS	1.76	(±4.37)	0.96	(±1.34)	0.79	(±1.18)	0.23	0.89

Note: The * symbol indicates significant (p<0.05) difference compared to HC, whereas $^{\#}$ marks significant (p<0.05) difference compared to the other patient group.

4.2.3. Correlations of clinical symptoms and WCST measures

MADRS scores of BD+ positively correlated with CLR% (r=0.36, p=0.047), negative symptom severity (r=0.55, p=0.003), general symptoms (r=0.82, p<0.001) and PANSS total score (r=0.73, p<0.001) (see Figure 8). No other significant correlations were found.

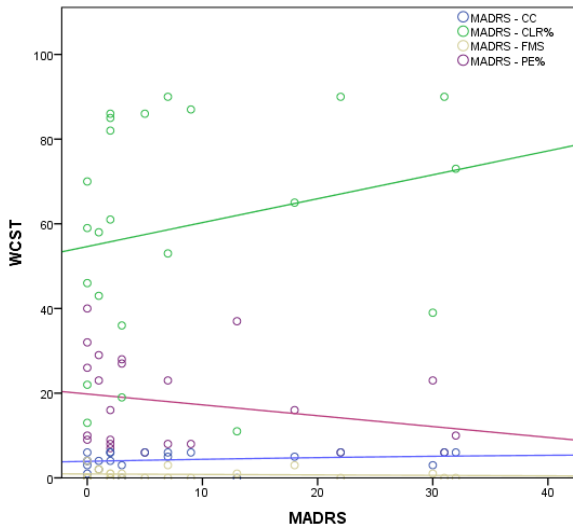

Figure 8. Correlations of WCST measures with MADRS scores of BD+ patients.

4.2.4. Correlations of demographic variables and WCST measures

The number of years spent in education and IQ scores had no correlation with WCST performance in the HC group, while patients with SZ with higher education accomplished more CC (r=0.35, *p*=0.04) and lower FMS (r=-0.52, *p*=0.003). In SZ IQ correlated positively with CLR% (r=0.37, *p*=0.03) and CC (r=0.44, *p*=0.018). In the BD+ group patients with more education had lower PE% (r=0.39, *p*=0.029) and higher CLR% (r=0.36, *p*=0.043). IQ level of BD+ patients had a negative relationship with the PE% (r=-0.57, *p*=0.002) and FMS (r=-0.4, *p*=0.028) and it was positively correlated with CLR% (r=0.6, *p*=0.001) and CC (r=0.54, *p*=0.004).

4.3. The relationship of ERPs and WCST

In the HC group FMS was correlated with the amplitudes of P3b (r=0.845, *p*=0.004) and dMMN (r=0.697, *p*=0.037); furthermore CC was in a negative relation with amplitude of P3b (r=-0.781, *p*=0.013) and dMMN (r=-0.677, *p*=0.045). In the SZ group only FMS correlated with N100 ratio (r=0.634, *p*=0.006). By BD+ patients no significant connections were revealed.

5. DISCUSSION

This thesis represents a complex approach to psychosis endophenotype research as it includes electrophysiological and neuropsychological measurements. The applied paradigms were chosen on the basis of the robustness of their dysfunction in SZ groups and in BD+ if ample data were present. The main aim was to grasp the pathomechanisms from central nervous system errors in auditory stimuli processing to behavioural deficits resulting in psychotic symptoms. We assumed that overlapping phenomenology of SZ and BD+ should be rooted in common neural and cognitive alterations, but to our surprise our results did not support the notion of a functionally connected and continuous psychosis spectrum.

In Study I it was assumed that patients with SZ and BD+ with psychotic features will show partially overlapping deficits in the included ERPs, but the results contradicted the hypotheses. The assumption, that P50 suppression and P3b parameters would be abnormal both in SZ and BD+ was not verified. Intact P50 suppression is a much unexpected result in SZ. Except for this the presumptions of Study I were underpinned, as N100 difference and dMMN latency and amplitude were impaired in SZ.

Corrupted P50 suppression is one of the most robust auditory ERP findings in SZ, earlier it was considered a candidate endophenotype for the disorder, but this was disproved. P50 gating can be improved via antipsychotic medication and nicotine administration (Brockhaus-Dumke et al., 2008). Atypical antipsychotics (Light et al., 2000), most of all clozapine have a normalizing effect on P50 suppression (Adler et al., 2004). In the present sample P50 gating in the SZ group was similar to that of HC. As the smoking status did not differ between the two groups, nicotine consumption could not be the reason for normal P50 suppression of SZ patients. Atypical antipsychotics might have a role in normal P50 measures, as 95% of the patients with SZ involved in Study I were treated with them, although only 20% was on clozapine. Some methodological issues could also contribute to normalized P50 gating. One of them is the applied filter range; we addressed this question by analysing the ERP with lower frequency bands filtered in and out. In both cases the P50 suppression in SZ remained intact. High signal-to-noise ratio is essential to get reliable data in ERP paradigms; it can be secured through repeated recording sessions from which data should be averaged (Boutros et al., 2009). The latter is lacking in our study, in the future this

option should be considered, although it is hard to accomplish due to ambivalent patient compliance.

In BD+ research regarding P50 suppression less data have been published than in SZ, but the available study results tend to show impaired sensory gating (Schulze et al., 2007; Sánchez-Morla et al., 2008; Carroll et al., 2008). The BD+ sample of Study I did not differ significantly from HC – or from SZ, although the averaged amplitude of the P50 elicited by S1 is smaller compared to the other two groups. This result is in line with the data reported by Brenner et al. (2009) according to which in SZ a sensory registration error can be described. The relatively small sample size could be the reason why this difference did not reach the appropriate level of significance. Smoking status was similar to the other two groups in BD+ and antipsychotic treatment was possibly not influencing the P50 waveform. Less than half of the BD+ patients (40%) were taking atypical antipsychotics and none of them was treated with clozapine. The medication of the BD+ group was quite heterogeneous making it harder to draw conclusions regarding the effects of medication on P50 suppression. Every person in the BD+ group was taking mood stabilizers, which are known to be neuroprotective agents (Paulzen et al., 2014), therefore might also normalize P50 gating effects.

Although the results of Study I contradict most of the data published regarding P50 suppression characteristics in SZ and BD+, the two patient groups did not differ in this sample. These participants were outpatients with pharmacologically ameliorated symptoms implicating relatively good functional level. If the possible correlation of clinical symptom severity, general functioning and P50 suppression is taken into consideration, this sampling bias could explain the intact P50 suppression in both patient samples.

In the presented study correlational analyses showed a strong relationship between positive, negative and manic symptoms and P50 suppression measures in the BD+ group. Symptom severity appears to be reducing P50 amplitude for S1, which is possibly disrupting the gating mechanism. This result is in line with sensory registration error theory (Brenner et al., 2009). It seems reasonable that sensory registration is related to symptoms; a longitudinal investigation might shed some light on the underlying factors.

Based on research data, the N100 suppression is also impaired in SZ (Salisbury et al., 2010) and our data are in accordance with this, although only the difference of S1 and S2 was altered compared to HC. Furthermore, the amplitudes related to S1 and S2 did not differ

among the groups, which points out that N100 generation and suppression reflect different neural mechanisms. Ours is not the first study to report dissociated impairment of P50 and N100 (Brockhaus-Dumke et al., 2008; Turetsky et al., 2009) pointing out that these two ERPs might have different neural bases despite their connected functions. More detailed research would be needed to clarify the influencing factors of early sensory processes.

In BD there is only scarce data regarding sensory gating; disrupted N100 along with P50 gating deficit was reported in one study (Lijffijt et al., 2009). Our BD+ group differed from that sample, as significantly higher ratio of our BD+ patients had a history of psychosis, the HC and patient groups were age matched and there were some medication differences, too. Thus, better patient-control alignment could be the reason for different results.

In a different paradigm N100 amplitude elicited by the onset of self generated speech sounds was not reduced in both SZ and BD groups, as it is by HC. There was no significant difference between patient groups; this can be regarded as a common dysfunction (Ford et al., 2013). Corollary discharge dysfunction reflected in N100 deficits might be a common characteristic for SZ and BD, but it is probably not a biomarker for psychosis, as unaffected relatives of the patients did not differ from HC (Ford et al., 2013). This paradigm is a more natural setting, resembling more real life dysfunctional processes compared to the 'paired-click' paradigm. This should be also considered when designing research paradigms. Although participants in our study were instructed not to pay attention to the sounds heard through headphones, they might have presumed that the click pairs have some kind of patterns, which might have oriented their attention towards them. Focused attention, even unconsciously can improve gating deficits.

In the MMN paradigm we examined ERPs elicited by duration and pitch deviant sounds, because dMMN seems to be a reliable trait marker in SZ, but results regarding pMMN are ambiguous (Umbricht et al., 2006, Salisbury et al., 2007; Näätänen and Kähkönen, 2009). In this sample pMMN was comparable to HC and dMMN amplitude was reduced in the SZ group. Furthermore, the latency of dMMN was significantly shorter in the SZ group, which has not been reported before. One study reported latency reduction of pMMN and a tendency for shortening of dMMN in SZ (Horton et al., 2011). More severe positive symptoms were correlated with MMN latency reduction and this was interpreted as a sign of disrupted temporal discrimination (Grzella et al., 2001). MMN latency might be

reduced by clozapine (Horton et al., 2011), but this cannot be the reason in the present sample, because only 20% of SZ patients was taking this antipsychotic agent.

The BD+ group in our study differed only in the prolonged pMMN latency from the HC group. Slower auditory information processing might be a general dysfunction in BD, as latency increments were reported for dMMN in BD-II (Andersson et al., 2008) and P3b in BD-I (Hall et al., 2009; Schulze et al., 2008).

Maybe the most replicated ERP deficit is the altered latency and amplitude of P3b both in SZ and BD, however, it is more underpinned in SZ. Our data are in line with the previous results regarding P3b amplitude in SZ; although latency was comparable to that of HC. Latency increments are more pronounced with longer disorder duration, crucial prolongations were observed after 20 years (Mathalon et al., 2000). Our SZ group's average illness duration was 13.44 years, which might explain the normal P3b latency.

BD+ patients in our sample showed almost no alterations in P3b characteristics. This might be due to their stable clinical status, as clinical symptoms can modify P3b (Turetsky et al., 1998). In this sample positive symptom severity prolonged the latency in both groups and decreased the amplitude of the waveform in BD+. Our results show that P3b alterations in psychotic disorders are related to positive symptoms, so this ERP deficit might not be a psychosis biomarker.

It was expected that patients with SZ will have more severe cognitive deficits measured with WCST than the BD+ group, which might be slightly impaired. This is what our results suggest, as BD+ patients could not be differentiated from HC, while the SZ group showed deficit in every measure of WCST except for FMS.

The positive correlation between depressive symptom severity and CLR% in BD+ group needs clarification, as it could be expected that more severe symptoms both in mania and in depression might disrupt cognitive processes. As the present sample showed mild depressive symptom severity, and it can be speculated that the somewhat slowed down thinking speed created more thorough solutions. Depressive symptoms can be interpreted as hyper-realistic thinking resulting in sharply appropriate observations and solutions. Nevertheless, this puzzling correlation needs further clarification.

Our results in Study II are in line with international research data (Seidman et al, 2002; Schretlen et al., 2007; Szoke et al., 2008). Patients with SZ show a more general cognitive impairment, while in BD verbal memory and executive functions are declined (Altshuler et al., 2004). The trait-like nature of executive dysfunction in BD is nevertheless not robust enough (Yatham et al., 2010). The cognitive functions measured through WCST are impaired in SZ groups compared to HC, which are independent from symptom severity (Sánchez-Torres et al., 2013; Ekerholm et al., 2012).

The present study also pointed out, that patients with SZ show more pronounced cognitive deficits than those with BD+. They performed worse on the WCST compared to HC measured by three parameters – PE%, CLR% and CC – and their ability to provide conceptualized responses was also weaker than the BD+ group's resulting in less completed categories. The differences in demographic variables and clinical symptom severity could not explain the cognitive performance patterns in the two patient groups. Therefore it can be assumed that these differences are independent from clinical state and are specific for both disorders. Some studies found correlations between negative symptom severity and WCST dimensions (Bagney et al., 2013; Rodriguez-Jimenez et al., 2013). The specificity of perseveration for SZ is still questionable (Waford & Lewine, 2010). Only years spent in school seemed to have some influence on the performance, but as the groups did not differ along this variable, this could not be the reason for the measured cognitive deficits. The relationship of education and WCST is still unclear (Ekerholm et al., 2012). Level of education seems to influence cognitive achievement differently from IQ, which points out the relative independence of school performance and IQ – at least in this sample. The higher average age (significance on a tendency level) of the BD+ group did not impact the WCST measures significantly.

The differences in WCST performance between the groups with SZ and BD+ were verified also by a quantitative review which reported that BD patients solved the task better than SZ patients in every included study (Krabbendam et al., 2005). The two disorders are divergent in this task so much that based on their performance first episode patients can be rendered into SZ, BD and other psychotic disorder groups with a certainty of 84.4% (based on 2 years follow-up) (Peña et al., 2011).

The neuropsychological and clinical similarities and differences might be explained by the theory suggested by Murray e al. (2004). According to their hypothesis there are genes

predisposing a general proneness for psychosis and genes causing disturbances during the course of neurodevelopment resulting in cognitive impairments in SZ. In BD presumably white matter decrements lead to non-specific cognitive dysfunctions (Bourne et al., 2013), which is also in line with the pMMN latency prolongation of BP patients in Study I. The main difficulty in comparing data from populations with BD is to find a sample with similar symptom severity, as the mood of BD patients usually fluctuates and influences the cognitive performance greatly. Euthymic patients have similar cognitive levels to HC groups according to most studies (Szoke et al., 2008; Fleck et al., 2008).

Based on the results of the involved studies the performance on WCST and auditory ERPs are not interrelated deeply. Compromised N100 suppression and FMS show strong correlation indicating that faulty sensory registration might result in missing important clues and choosing inappropriate strategies. Surprisingly, P3b waveform alterations in SZ were not related to their poor performance on WCST. Correlational analyses in HC resulted in puzzling data, as they indicate that bigger amplitudes of P3b and dMMN are present in individuals who perform worse in WCST. Nevertheless this correlation would possibly be different if the HC group would consist of more people. In the future more cognitive tests should be administered to bigger samples in order to get enough data for the clarification of these correlations.

6. GENERAL CONCLUSIONS

Although many genetic, biological and clinical features are common in SZ and BD, research data are still controversial regarding the etiological relevance of this overlap. These ambiguities are in part due to methodological differences between laboratories, e.g. sample inclusion criteria, which might result in heterogeneous patient groups. In the case of BD it would be essential to indicate whether patients with or without psychotic symptoms were included. The data presented here aimed to overcome methodological and patient heterogeneity, therefore the procedures were applied under the same circumstances on groups representing both disorders and only BD patients with a history of psychosis (BD+) were included.

According to our data there were no shared ERP deficits in the SZ and BD+ groups indicating different underlying neural processing dysfunctions of auditory stimuli. As N100 suppression, dMMN parameters and P3b amplitudes were dissociated in the two psychotic disorders, we can assume that different mechanisms play role in the development of psychotic symptoms in SZ and BD+. Study I is the first report of shorter latency of dMMN in patients with SZ; however, the underlying mechanisms need further research to be clarified. Nevertheless, ERP indices are only a part of dysfunctional processes in mental disorders, so it is advisable to investigate other levels of psychological functioning and to search for links between them to get a more precise picture.

Based on the presented results the WCST is not only a valuable tool to measure the deficits in SZ compared to HC, but also eligible to differentiate between patients with SZ and BD+ according to their cognitive performance. The disorders affect cognitive – executive – functions differently, which should be considered in the choice of interventions and could be implemented in the assessment of prognosis and diagnostics, too.

According to our data SZ and BD+ have dissociated auditory ERP deficits compared to HC. Furthermore the two patient groups show highly differentiated executive function performance as BD+ patients show intact WCST measures. The indices of neurophysiological processing of auditory stimuli and set-shifting ability were only slightly interrelated; this points out the distinct processes underlying cognition and perception.

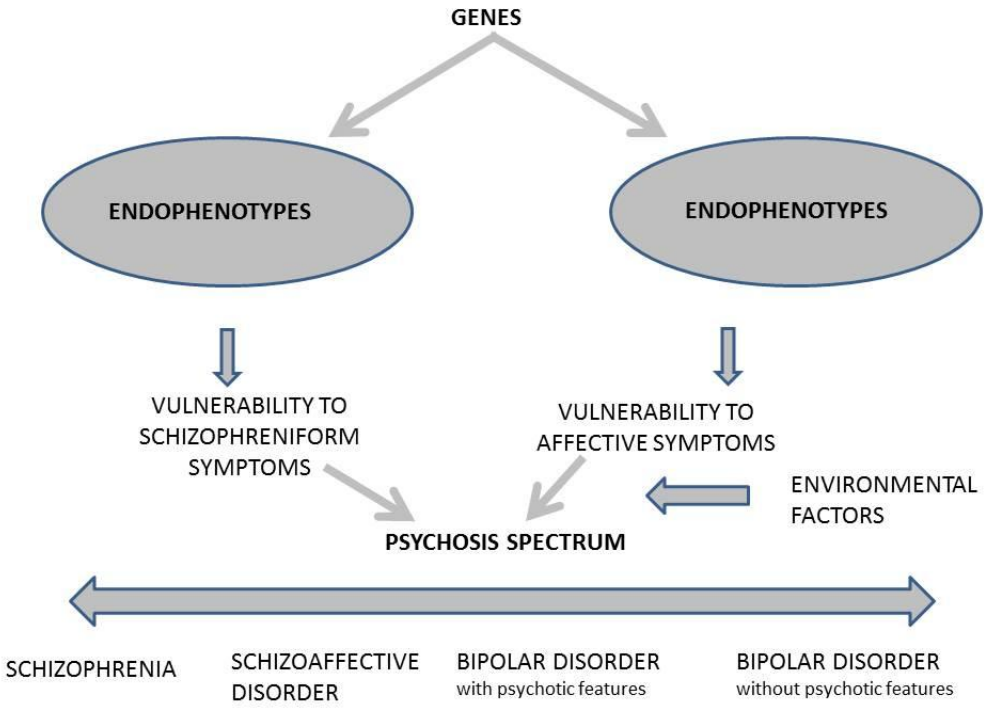

Figure 10. Simplified model of the involvement of separate endophenotypes in the development of different mental disorders with psychotic features.

The presented data contradict the notion of a psychosis spectrum on which SZ and BD+ represent different severity levels, as there was no significant overlap in their psychophysiological and cognitive functioning. Based on the results of Studies I and II, it can be concluded that psychotic symptoms are the results of different neurophysiological processes. Various dysfunctions may result in similar symptomatology. Alternatively, the common underlying causes of psychosis in SZ and BD are not reflected in ERP measures; this can be addressed by applying various methods to reveal shared neurophysiological alteration. Figure 10 models the involvement of different endophenotypes' pathways in generating similar and even overlapping symptoms.

There are some limitations of the presented studies, of course. The sample size should be increased in order to secure the validity of the measurements and conclusions. The inclusion of clean diagnostic groups was of priority. Furthermore patients with severe functional deficits are less willing to participate in studies, and they reach a level of symptom remission harder, therefore they might be missing in representative numbers. The heterogeneity of symptoms in each acute phase and the heterogeneous medication makes it difficult to create clean study groups and to interpret the resulting data. A possible solution for

this problem is to involve great samples, even from more research sites – this is part of the future plans of our research group.

Research conducted so far by our team did not manage to demonstrate results underpinning the notion of a psychosis spectrum on which SZ and BD represent different severity levels, as there was no significant overlap in their psychophysiological and cognitive functioning. It is possible that among the several genes predisposing psychotic disorders there are some connected to neurocognitive disturbances and others connected to emotional regulation. The resulting endophenotypic variations might be definitive of dominant clinical symptoms and distinctive in different mental disorders. The detailed research on ERPs and cognitive dysfunctions in mental disorders may help to better understand the aetiology of them and to create more appropriate screening and treatment methods.

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APPENDIX