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

PhD Thesis

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Introduction

Psychosis is a syndrome presenting in various mental disorders, most commonly in schizophrenia (SZ) and bipolar affective disorder (BD). As these disorders disrupt the everyday functioning of the patients, it is essential in psychiatric research to provide explanations for their development in order to help the identification of possible treatment targets. In SZ genetic, neuromorphologic and functional alterations, cognitive, emotional and behavioural dysfunctions have been revealed and studied thoroughly. Data regarding patients with BD are more controversial, although quite similar disturbances have often been demonstrated as in SZ. The overlapping findings resulted in the notion that SZ and BD might constitute two parts of a continuous psychosis dimension. In the recent decades research aims to provide convincing evidence pro or contra this theory.

Endophenotypes might provide appropriate tools for the definition of risk and aetiological factors for mental 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. Event-related potentials (ERPs) and cognitive deficits are among the candidate shared endophenotypes of SZ and BD, although the regarding results are still controversial.

In this ongoing scientific debate the gathered data are in favour of the dimensional approach, but the 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.

Auditory event-related potentials as candidate endophenotypes of psychotic disorders

The main part of the present thesis focuses on ERPs in patient groups with SZ and BD with anamnestic psychotic symptoms (BD+). The electric change due to the neuronal activity elicited by a stimulus can be observed on the electroencephalogram (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. Among the most commonly studied ERPs in psychotic disorders are P50 suppression, N100 suppression, P3b (and P3a) and the mismatch negativity (MMN).

P50 is a positive waveform occurring 40-75 ms after the stimulus onset; its amplitude is usually defined compared to 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 waveform. This suppression effects enables to screen out irrelevant stimuli. The measurement of suppression can be quantified through the difference or the ratio of the amplitudes elicited by the first stimulus (S1) and the second (S2) – and the ratio seems to be more reliable. If gating mechanisms are disrupted, stimuli flood the processing systems of the brain leading to e.g. false or hyper-perception manifesting in the form of hallucinations. There is a vast amount of data demonstrating faulty P50 suppression in SZ groups. Scientific results tend to confirm P50 suppression deficit as a common feature in both SZ and BD, although the degree of deficit in P50 suppression might differ by SZ and BD groups.

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 and also shows the suppression effect. The N100 suppression deficit seems to be developing gradually along the progression of SZ.

The MMN is regarded as the electrophysiological representation of auditory discrimination, automatic change detection and echoic memory. MMN is triggered by an irregular sound in a train of stimuli. 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. 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. The dMMN amplitude reduction is considered as the most robust endophenotype candidate in SZ. In BD+ studies report no significant differences compared to healthy controls (HC). 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 ultra-high risk groups.

Actively attended target stimuli generate the P3b waveform, which might represent the content updating of working memory based on the contextual information. The magnitude of the amplitude reflects the difficulty of the task, while the latency depends on the speed of information processing. The deficit of P3b is regarded as one of the endophenotype candidates in SZ. In BD P3b amplitude is diminished and latency is prolonged, which is also

measurable in unaffected relatives. P3b amplitude deficit might be a psychosis endophenotype and not a specific biomarker, although the clinical state might influence the characteristics of P3b.

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 and BD, even though their results are controversial. These discrepancies might be results of differences in stimulus parameters, attention, arousal, smoking status or psychotropic medication, 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 inter-related, therefore ERPs might as well reflect distinct perceptional functions.

Executive dysfunctions as candidate endophenotypes of psychotic disorders

Stimulus processing dysfunctions might be observed on the behavioural level via cognitive disturbances. 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. In BD+ the data regarding cognitive deficits are contradictory and hard to replicate due to the heterogeneity of the samples. 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. 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.

Among the different layers of cognition 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. Many measurement methods have been developed based on different theories. One of the most widely used tests for the measurement of working memory functions and shifting ability is the Wisconsin Card Sorting Task (WCST). Shifting function measured by the means of WCST is disrupted in SZ based on robust research data, while in BD results are ambiguous.

Only few studies are at hand regarding the correlations of neurocognitive measures and ERPs; and they present heterogeneous data. Many factors need to be clarified regarding auditory ERPs and their relations to clinical symptoms and cognitive functioning is psychoses. The processes through which early neurobiological dysfunctions manifest as cognitive deficits or clinical symptoms might provide pharmacological and therapeutic targets.

Aims

Study I focused on ERP characteristics of the auditory stimulus processing in SZ, BD+ and HC groups and their relationships to clinical symptom severity. According to the scientific results published so far we expected that P50 suppression and P3b parameters would be abnormal both in SZ and BD+, while N100 suppression and MMN (primarily dMMN) would be impaired in SZ. The relationship of ERPs and clinical symptom severity was of special interest, as this provides valuable information about the validity of the included ERPs as trait characteristics in psychotic disorders.

Study II investigated executive functioning by the means of WCST involving patients with SZ and BD+ and HC people. 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.

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.

Methods

Participants

In Study I N=20 patients with SZ, N=20 with BD+ and N=21 HC subjects were enrolled. In Study II N=26 SZ and N=24 BD+ patients' data were compared to the performance of N=21 HC. The two samples were partially overlapping; the merged sample of HC contained the less people who participated in both studies. Based on clinical screenings every patient met DSM-IV criteria for the relevant disorder and HC participants were free of any mental disorders. Smoking status was obtained by self-reporting the number of cigarettes smoked per day. Substance abuse or dependence (except for nicotine and caffeine) in the preceding 12 months was an exclusion criterion. 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 and testing sessions. The protocol was approved by the Ethics Committee of the University of Szeged. The investigators were not blind regarding the clinical diagnoses of the participants.

Clinical symptom assessment

The interviews for the Positive and Negative Symptoms Scale (PANSS), Young Mania Rating Scale (YMRS) and Montgomery–Åsberg Depression Rating Scale (MADRS) were conducted at the time of examination to assess clinical symptom severity in SZ and BD+ groups. The HC group was screened for psychiatric disorders by a trained psychiatrist and a psychologist through the Mini International Neuropsychiatric Interview 4.4 (MINI) and the Structured Clinical Interview for DSM-IV Axis II (SCID-II).

EEG registration and ERP paradigms

The recordings were performed in a sound-proof, electrically shielded room. 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 (all 110 dB SPL, 0.1 ms) that were separated by 500 ms stimulus intervals. 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 with a stimulus-onset asynchrony 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 stimulus onset asynchrony of 1 second, and our subjects were asked to count the target ones silently. The recording was considered successful only if the counting error percentage was below 10%. One BD+ patient did not count correctly, so her data was excluded from the P3b analysis.

Recordings were done with a Nicolet Bravo Multimodality System. Nineteen tin scalp electrodes mounted in an elastic cap were placed in accordance with the international 10/20 system. 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.

On the continuous EEG data segmentation, baseline correction, artifact rejection and appropriate filtering methods were conducted. After averaging, ERP amplitude and latency parameters were measured manually. For defining the P50 and N100 waves, peak-to-peak amplitudes were calculated; 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. The P3b was assessed at electrode Pz as the largest positivity between 300-500 ms for potentials obtained for the target tones (amplitude computed from baseline).

WCST – measurement of executive functions

In Study II the manual (paper-pencil) version of WCST was used. 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%).

Statistical analyses

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.

In Study I 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 as within-subject factors, group as between subject factor and smoking as covariate. 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's correlation was applied to reveal any relationships among ERP measures and clinical symptom severity.

In Study II Shapiro–Wilk test was applied to examine the normal distribution of the data. 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.

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

Results

Study I

Demographic and clinical characteristics

Regarding the demographic characteristics (Table 1) the groups differed only in years spent in

school (HC vs. 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.

ERP characteristics

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. S1 and S2 amplitude, P50 gating ratio and difference values were not significantly different either, regardless of the low-pass filter setting. Regarding the N100 a weak, but statistically

significant alteration between SZ and HC values (p=0.048) of N100 difference was revealed. Neither N100 ratios nor S1 and S2 amplitude values did differ between the three groups.

The comparison of the HC and SZ data revealed a significant difference ($F_{1,36}$=6.281; p=0.017) with smaller dMMN amplitudes in SZ (see Table 2). Patients with SZ demonstrated shorter latencies of dMMN when compared to HC ($F_{1,36}$=4.349; p=0.044) and BD+ ($F_{1,34}$=9.364; p=0.004). P3b amplitudes were smaller 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). 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.

Study II

Demographic and clinical characteristics

There were no significant differences among SZ, BD+ and HC groups in the involved socio-demographic values (see Table 3). PANSS scores of the two patient groups differed significantly only in the negative and total subscales, the SZ group showed more severe symptoms. For detailed data see Table 4.

Table 3. Socio-demographic 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

Executive functioning

Performance on the WCST was significantly different when comparing SZ, BD+ and HC groups. 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. For exact data see Table 4.

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.

Correlational analyses

In the SZ group only the latency of P3b and the positive symptom severity 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 was only correlated 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).

PANSS and WCST scores had no correlations in the SZ group. 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). In the SZ group only FMS correlated with N100 ratio (r=0.634, p=0.006). By BD+ patients no significant connections were revealed.

Discussion

We assumed that overlapping phenomenology of SZ and BD+ should be rooted in common neural and cognitive alterations, but our results did not provide supporting data for the notion of a functionally connected and continuous psychosis spectrum.

Intact P50 suppression is a much unexpected result in SZ. P50 gating can be improved via antipsychotic medication – mostly clozapine and nicotine administration. 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 these effects need more detailed analysis and more homogenous patient groups. The BD+ sample of Study I did not differ significantly from HC – or from SZ. Smoking status was similar to the other two groups in BD+. Less than half of the BD+ patients (40%) were taking atypical antipsychotics. The medication of the BD+ groups was quite heterogeneous rendering it harder to draw conclusions regarding the effects of medication on P50 suppression.

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, and it is possibly disrupting the gating mechanism. A longitudinal investigation might shed some light on which is primary; even mild symptoms could distract the sensory processing system from incoming new stimuli, or faulty registration processes might result in false perception and incoherency.

Our data are in accordance with results suggesting impaired N100 suppression in SZ, 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.

In this sample of patients with SZ pMMN was comparable to HC and dMMN amplitude was reduced. Furthermore, the latency of dMMN was significantly shorter in the SZ group, which has not been reported before. Duration deviant tones are easier identified, but it is unclear, why patients with SZ react to them faster than HC participants. The BD+ group in our study differed only in the prolonged pMMN latency from the HC group; this can be regarded as a sign of slower auditory information processing.

Our data are in line with the previous results regarding decreased P3b amplitude in SZ; however latency was comparable to that of HC. Latency increments are more pronounced with longer disorder duration. Our SZ group had an average illness duration of 13.44 years, which might partly explain the normal P3b latency. BD+ patients in our sample showed almost no alterations in P3b characteristics; this might be due to the fact that they were in a remission, as clinical symptoms can modify P3b. In this sample positive symptom severity was correlated with the latency in both groups and decrement of the amplitude of P3b 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.

Based on the results of Study II BD+ patients could not be differentiated from HC and 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 further clarification. 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, it could 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.

According to our data 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 poor performance on WCST.

Outline of main results

Intact P50 waveforms and P50 suppression in SZ is a rare result; however it might be due to sampling bias or medication. Nevertheless this result contradicts its role as a biomarker for SZ.

Dissociated impairment of P50 and N100 points out that these two ERPs have different neural bases despite their connected functions. Components of auditory perception and screening mechanism might be affected differently in SZ indicating multiple dysfunctions in the background of clinical symptoms.

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.

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.

The cognitive performance pattern of the two patient groups was also dissociated, that is the SZ group having more difficulties in set-shifting.

Clinical symptoms and indices of executive functioning showed different connections to ERP characteristics in groups with SZ and BD+. This sheds some light on the possible different pathways between perceptional processing, cognition and clinical symptoms.

Based on the presented results the WCST and ERPs reflecting sensory gating are not only valuable tools to measure the deficits in SZ compared to HC, but also eligible to differentiate between patients with SZ and BD+. This could be applied in early identification of people at ultra-high risk for psychosis.

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.

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PAPERS THE THESIS IS BASED ON:

I. Domján N, Csifcsák G, Drótos G, Janka Z, Szendi I. Different patterns of auditory information processing deficits in chronic schizophrenia and bipolar disorder with psychotic features. Schizophr Res. 2012;139(1-3):253-259. doi:10.1016/j.schres. 2012.06.002. IF: 4.43

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