Event-related potentials and use of psychotropic medication in major psychiatric disorders

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ABSTRACT

Background: Attention deficits measured using event-related potentials (ERPs) have been frequently reported in several major psychiatric disorders, e.g. mood disorder (MD), psychotic disorder (PD) and substance use disorder (SUD). However, comparisons between these specific categories are lacking. Here we investigated if electro-physiological parameters of basic information processing are associated with the above-mentioned categories of psychiatric disorders, or instead were associated with general psychopathology.
Methods: 579 subjects with MD, PD or SUD and healthy controls (HC) were included. Participants were tested in a passive auditory and an active visual oddball paradigm to assess mismatch negativity (MMN), P3A and P3B amplitudes. Additionally, we examined associations between these measures and psychoactive medication treatments.
Results: All patients had significantly lower P3B amplitudes compared to healthy controls, while only SUD patients had lower P3A amplitudes than MD, PD and HC. PD patients also produced significantly less MMN than both MD and SUD patients. Additionally, we found significantly higher P3B amplitude in HC compared to patients without psychopharmacological treatment and patients treated with two or more psychoactive compounds (polypharmacy), but no significant associations with medication on P3A and MMN amplitudes.
Conclusions: Our results add to the theory that P3B deficits are associated with general psychopathology, whereas P3A and MMN deficits appear to be associated with substance abuse and psychotic disorders respectively.

1. Introduction

Deficient information processing is one of the key features of several major psychiatric disorders. For instance, deficits in selective attention and mismatch negativity (MMN) are frequently reported in schizophrenia, mood disorders and substance use disorders (Näätänen, 1990).

One of the electrophysiological components of selective attention is the P300 amplitude. The P300 amplitude consists of an early component, the P3A amplitude, and a later component, the P3B amplitude. The P3A amplitude is elicited whenever the brain detects a novel stimulus in a series of standard stimuli, and is thought to be related to the preceding

orienting reflex, which in turn is believed to be represented by MMN. The P3A amplitude and MMN can both be assessed with a *passive* oddball paradigm, in which a series of frequent (standard) and infrequent (oddball) stimuli is presented in an alternating fashion and where no response of a subject is required. MMN is the negative deflection appearing in the Electroencephalography (EEG) as a result of the brain's detection of the infrequently presented stimulus that deviates in some physical features from the repeatedly presented (standard) stimuli. MMN is considered to reflect the subconscious auditory change detection based on memory and comparison processes (Näätänen, 1995), and as such is often referred to as an orienting reflex. MMN is usually

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followed by a P3A amplitude, which is thought to reflect an update in working memory when changes in the environment occur (Donchin and Coles, 1988; Polich, 2007; Polich and Criado, 2006). In contrast to the P3A amplitude which requires no active attention from a subject, the P3B amplitude is more task-related, i.e. it requires a response. The P3B amplitude is therefore often assessed in an *active* 'oddball' paradigm, wherein a subject is asked to respond to the infrequently occurring oddball stimulus (hence *active* oddball), maximizing its amplitude (Polich, 2007; Polich and Criado, 2006; Picton et al., 2000).

Deficits in MMN, P3A and P3B amplitude have been frequently reported in major psychiatric disorders, such as schizophrenia (e.g. (Kruiper et al., 2019; Jeon and Polich, 2003; Rydkjær et al., 2017; Umbricht and Krljes, 2005)), bipolar disorder (Nan et al., 2018; Röschke and Wagner, 2003; Wada et al., 2019) and substance use disorders (SUD) (Enoch et al., 2001; Hamidovic and Wang, 2019). MMN findings in major depression disorder (MDD) are inconsistent (Umbricht et al., 2003; Lepistö et al., 2004; Qiao et al., 2013) and seem to depend on the type of deviant stimulus: pitch-based deviant stimuli in MDD patients trigger responses similar to those observed in healthy volunteers, whereas higher intensity deviants produce higher levels of MMN compared to healthy volunteers (Bissonnette et al., 2020; Bonetti et al., 2017). The same applies for alcohol use disorders (AUDs) (Polich et al., 1994; Ramachandran et al., 1996) where results were incongruent (Fein et al., 2004; Marco-Pallarés et al., 2007).

Although event-related potentials (ERPs) have been suggested to index general psychopathology (Bramon et al., 2005; Hamilton et al., 2019), comparisons of MMN and P300 amplitude between psychiatric disorders (such as schizophrenia, SUD and MDD) are lacking. This knowledge gap currently hampers insight into the generalizability of these markers for psychiatric disorders.

MMN and selective attention appear to be modulated by several neurotransmitters: MMN by glutamatergic, serotonergic and noradrenergic neurotransmission (e.g. Oranje et al., 2008; Wienberg et al., 2010; Kruiper et al., 2019b; Javitt et al., 1996), which also appear to be involved in MDD (Nutt, 2008; Chiriţă et al., 2015), schizophrenia (Yang & Tsai, 2017) and SUD (Kreple et al., 2014; Lovinger, 2008); P3A amplitude mainly by dopaminergic neurotransmission, which is also known to be affected in schizophrenia patients (Polich, 2007; Yang & Tsai, 2017); while the P3B amplitude, similar to MMN, is modulated by glutamatergic and noradrenergic neurotransmission (e.g. Polich, 2007; Oranje et al., 2009; Oranje et al., 2000). Not surprisingly therefore, medication is known to affect these ERP waveforms. Literature reports reduced P3A&B amplitudes and enhanced MMN following administration of, respectively, benzodiazepines (Fukami et al., 2010; Semlitsch et al., 1995) and antidepressants (Wienberg et al., 2010; Jaworska et al., 2013; Liogier D'Ardhuy et al., 1999) to healthy subjects. However, the reported effects of medical treatment in psychiatric patients are rather inconsistent. For instance, some studies do report effects of antipsychotics on either P3B (Umbricht et al., 1998) or MMN (Zhou, Zhu, & Chen, 2013) amplitude, while others observed no such effects on these amplitudes (Oranje et al., 2017; Kruiper et al., 2019b). These inconsistencies are probably related to differences in receptor profiles of the antipsychotics that were used or, more specifically, related to differences in their affinity for the dopamine D_2 and serotonin 5-HT$_{2A}$ receptors (Meltzer, Li, Kaneda, & Ichikawa, 2003).

The aim of this project was to investigate whether the abovementioned electrophysiological parameters of basic information processing (MMN, P3A and P3B amplitudes) are associated with specific types of psychiatric disorders, or instead with broad psychopathology. We therefore collected a relatively sizeable study population of patients suffering from three major categories of psychiatric disorders (mood disorders, psychotic disorders and substance use disorders) and exposed them to a passive auditory and an active visual oddball paradigm. We then compared the electrophysiological measures across the different (sub) diagnoses as well as to a group of healthy volunteers. Additionally, we examined the associations between psychotropic medication and

these measures. We expected to find significant variance in MMN, P3A and P3B amplitudes between disorders that could extend our knowledge on associations between ERPs and several severe psychiatric disorders.

2. Experimental procedures

2.1. Study population

ERP recordings were collected from 579 patients and healthy controls at Ziekenhuis Netwerk Antwerpen (ZNA), a large community hospital in Antwerp, Belgium. We abided by the principles laid out in the Declaration of Helsinki (9th July 2018). The study was approved by the Institutional Review Board of ZNA and all participants provided written informed consent.

To increase the likelihood of severe burden of disease, only hospitaladmitted psychiatric patients were included. Additional inclusion criteria were: adults (age $\geq$ 18 years); at least one of the following main psychiatric classifications that were established using clinical diagnostic interviews according to DSM-IV-TR criteria: mood disorder (MD, depressive and bipolar disorder, all DSM classifications except for MD due to medical condition or substance use), psychotic disorder (PD, schizophrenia or other psychotic disorder, all DSM classifications except PD due to a medical condition or substance use) and substance use disorder (SUD, alcohol and/or drug use disorder). The presence of other psychiatric comorbidities was no exclusion criterion if they were rated by the clinician as a non-primary diagnosis, i.e. the main classification was defined as the disorder being most important in that patient as well as being the reason for admission for that patient (see also Table 1). For example, a patient with a history of a mood disorder who was admitted with an SUD and in whom the SUD was judged as the primary diagnosis, was included in the SUD category and not the mood disorder category.

Healthy controls (HC) were defined as having no current psychiatric

Table 1
Demographics; Age, sex, diagnosis and medication use of the experimental groups

	HC		Patients		*p*
	P300 (n=31)	MMN (n=46)	P300 (n=439)	MMN (n=533)	
Mean age *(SD)*	23.68 *(2.71)*	24.93 *(5.99)*	41.77 *(12.55)*	41.07 *(12.52)*	p < .01*
Sex (m/f)	15/16	18/28	250/188	295/238	p>.34 * n.s.
Questionnaires (Yes/No)	–	345/94	419/114		
Main diagnose (MD/ PD/SUD)	–	203/61/ 175	256/72/ 205		
Benzodiazepine use (Yes/No) (within MD,PD,SUD)	–	169/255 (93/103, 42/19, 34/133)	197/336 (111/139, 50/22, 36/ 161)		
Antipsychotic medication (first generation/ second generation) (within MD, PD, SUD)	–	21/157 (8/56, 6/ 54, 7/47)	27/192 (11/67, 6/ 65, 10/60)		
Antidepressant (SSRI/SNRI/TCA/ NDRI) (within MD, PD, SUD)	–	122/139/ 41/9 (71/ 62/24/5, 13/5/4/ 0, 38/72/ 13/4)	146/161/ 53/13 (86/ 80/32/7, 15/4/4/0, 45/77/17/ 6)		

Abbreviations: MD=Mood Disorder, PD=Psychotic Disorder, SUD=Substance Use Disorder, UMD=Unipolar Mood Disorder, BMD=Bipolar Mood Disorder, PDU=Psychotic Disorder Unspecified, PDS=Psychotic Disorder Specified, PDD=Psychotic Delusional Disorder, SUDA=Substance Use Disorder Alcohol, SUDD=Substance Use Disorder Drugs.
* removing the healthy controls gives a p>.129 for age and p<.01 for gender.

episode and never been treated in a mental health service.

To assess severeness of psychopathology, all patients were requested to fill in one or two questionnaires corresponding to their psychiatric diagnosis or symptoms. These questionnaires included the second version of Beck Depression Inventory (BDI-II) for MD, and additionally the Dutch Mood Disorder Questionnaire (MDQ-NL) if a bipolar disorder was present or could not be ruled out; the brief Schizotypal Personality Questionnaire (SPQ-brief) for PD; Alcohol Use Disorders Identification Test (AUDIT) and/or Drug Abuse Screening Test (DAST) for alcohol and other substance use disorders, respectively. Participants were first exposed to an active visual oddball paradigm (assessing the P3B amplitude) and a passive auditory oddball paradigm (assessing MMN and the P3A amplitude); then they filled out the questionnaires. Given that the active oddball paradigm was somewhat later introduced in this project, 579 patients were assessed with the passive oddball paradigm, whilst 470 were additionally assessed with the active oddball paradigm (see also Table 1).

2.2. Paradigms

2.2.1. Active oddball

The visual active oddball paradigm consisted of 200 stimuli that were presented during seven minutes of recording. Two types of stimuli (O and X, both 1000 ms, white colored on black background with a font size of 124) were presented in the center on a computer screen in front of the participants: an "O" being the standard stimulus occurring with a probability of 80% of the cases and an "X" which was the target (oddball) stimulus appearing, in 20% of the cases. Participants were asked to press 1 with their index finger when the "O" stimulus was presented and press 2 with their middle finger when the "X" stimulus was presented.

2.2.2. Passive oddball

The passive oddball paradigm consisted of a series of 1930 auditory stimuli presented in a random fashion. Participants were instructed not to pay attention to stimuli when the stimuli were presented. Four types of stimuli were presented: a standard stimulus (a "da" of 170 ms) presented in 83% of the cases, and two deviant stimuli (a "ta" and "tha" of 170 ms) both presented in 8% of the cases as well as a rarely occurring deviant stimulus (a "beep" of 1000 Hz and 170 ms) in 1% of the cases. Deviants were never presented in direct succession.

2.3. Data processing

ERP recordings were made using a 64-channel Electrical Geodesics Incorporated (EGI) system, Philips, USA. Only data from the relevant electrodes (where maximum amplitude was reached) were analyzed for the present study, i.e. midline electrode FCz for MMN and P3A amplitude, and midline electrode Pz for P3B amplitude, with average reference. A standard method of data processing was used: BESA software (version 6.1, MEGIS Software GmbH, Gräfelfing, Germany) was used for processing the EEG signals. To allow easier file handling, the data was first down-sampled from the original 500 Hz to 250Hz. Second, data were corrected for eye-artifacts using the adaptive method of BESA. Third, the data were epoched (from 100ms pre-stimulus to 900ms post-stimulus) and corrected for movement and other paradigm unrelated artifacts, by removing those epochs that contained amplitude differences that exceeded 75μV between the maximum and minimum in the for MMN assessment relevant time window. Last, data were band-pass filtered (0.5Hz - 40Hz). MMN was expressed as a subject's average ERP to each of the 3 deviant stimuli from which the average ERP to the standard stimuli was subtracted. MMN was scored as an individual's maximum negative voltage appearing in the EEG within a time window between 130-230ms for the beep stimulus, and between 140-260 ms for the other two deviant types. Similarly, an individual's P3a amplitude was scored as the maximum positive amplitude in a time window

between 200 and 370 ms (all three types of deviants) while the P3B amplitude was assessed as the maximum positive amplitude between 330 and 600 ms.

2.4. Statistical analyses

All statistical analyses were carried out using SPSS Statistics version 25.0 (SPSS Inc., USA). Outlying values were Winsorized (truncated) to 2 SD from the group average, to minimize their effects. Due to this Winsorizing, nearly all data reached normal distribution (Kolmogorov-Smirnov test p>0.05), with only few exceptions; whenever post-hoc tests (see below) indicated significance in inferential statistics for these exceptions, these results were confirmed by non-parametric Mann-Whitney tests. First, to screen for initial group differences, the data of the passive oddball paradigm were analysed by a multiple analysis of covariance (MANCOVA) for MMN and P3A separately, with between factors "Group" (healthy controls or patients with MD, PD or SUD) and within factors "Deviant" (ta (deviant 1), tha (deviant 2) or beep). Similarly, the P3B data of the active oddball was analysed with MANCOVA with between factor "Group" and within factor Stimulus (standard (O) or deviant (X)). We also performed these analyses for several distinct sub diagnoses of the above mentioned 4 major diagnostic categories of patients (MD; Unipolar Mood Disorder (UMD) and Bipolar Mood Disorder (BMD), PD; Psychotic Disorder Unspecified (PDU), Psychotic Disorder Specified (PDS) and Psychotic Delusional Disorder (PDD) and SUD; Substance Use Disorder Alcohol (SUDA) and Substance Use Disorder Drugs (SUDD)), which are presented in the supplemental material. Differences between pharmacological treatments with regards to the 3 electrophysiological components was analysed with MANCOVA with between-factors "Treatment" (healthy controls not on medication, patients not treated with medication, patients treated with benzodiazepines only, patients treated with antipsychotics only, patients treated with antidepressants only or patients treated with a combination of those). For the interested reader we also present data on associations with several specific subtypes of medication (antipsychotics: first generation and second generation; and antidepressants: Selective Serotonin Reuptake Inhibitor (SSRI), Serotonin–norepinephrine reuptake inhibitors (SNRI), Tricyclic antidepressants (TCA) and Norepinephrine–dopamine reuptake inhibitor (NDRI)) in the supplemental material. Age and gender were used as covariates in all analyses, but removed from the analyses when they did not contribute significantly; this was the case for MMN and P3B amplitude, however not for the P3A amplitude, where age and gender covaried significantly. To reduce chances of type-I errors, post-hoc tests (Tukey) were only performed whenever the MAN(C)OVAs showed significant results; p<0.05 was used as a threshold for statistical significance in all tests. Last, for the entire study population and then for each main diagnosis group, we performed correlation analyses (Spearman) between symptom severity (z-scores of the above-mentioned psychopathological rating scales) and the electrophysiological measures to explore potential associations between the symptom severity and the ERPs.

3. Results

3.1. Subjects

The healthy controls were significantly younger than the other diagnostic groups (p<0.01), who in turn did not differ significantly in age from each other (p=0.2). Group differences in gender were nonsignificant when including the healthy controls (p=0.3), yet when removing the healthy controls there was a significant difference across the groups (p<0.01, see Table 1, also for more demographics including pharmacological treatment).

3.2. SA paradigm

3.2.1. ERP differences between diagnosis

We found main effects of Group ($F_{1,462}=2.73$; $p=0.043$, $\eta^2=0.017$) and Stimulus ($F_{1,462}= 28.67$; $p<0.001$, $\eta^2=0.058$), as well as a Stimulus*Group interaction ($F_{3,462}=3.07$; $p=0.028$, $\eta^2=0.020$) on P3B amplitude; post-hoc tests showed that all 3 major patient groups scored significantly less P3B amplitude than controls to target stimuli only ($p<0.036$, see also Figure 1A), while the patient groups did not differ significantly from each other ($p>0.091$). No significant group
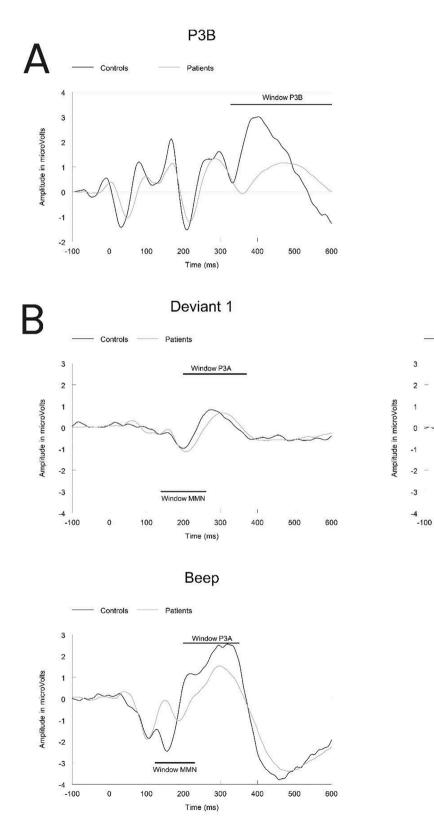

Fig. 1. Grand average waveforms of controls and patients for (A) the P3B amplitude of the SA paradigm at electrode Pz and (B) each of the three deviants of the MMN paradigm at electrode FCz. The bars indicate the windows in which the different ERPs of the individuals were scored.

differences in P3B amplitude were found for standard stimuli (p>0.618) (see also Figure 2A). For results on subcategories of patients see supplemental materials and figure S1A.

3.2.2. ERP differences between medication categories

We compared P3B amplitude between patients who were treated with and without a certain psychotropic type of medication. We found significant main effects of Treatment ($F_{5,422}=2,59$; $p=0.025$, $\eta^2=0.017$) and Stimulus ($F_{1,422}= 84.88$; $p<0.001$, $\eta^2=0.167$), as well as a significant Stimulus*Treatment interaction ($F_{5,422} =2.73$; $p=0.047$, $\eta^2=0.026$). Subsequent post-hoc tests showed no significant effects of treatment on P3B amplitude to standard stimuli ($p=0.16$), but significantly higher P3B amplitudes to targets in healthy controls than either in patients treated with no medication at all ($p=0.014$) or patients treated with a combination of two or more types of medication ($p<0.001$; see Figure 2B). For findings on specific subtypes of medication see supplemental material and figure S1B.
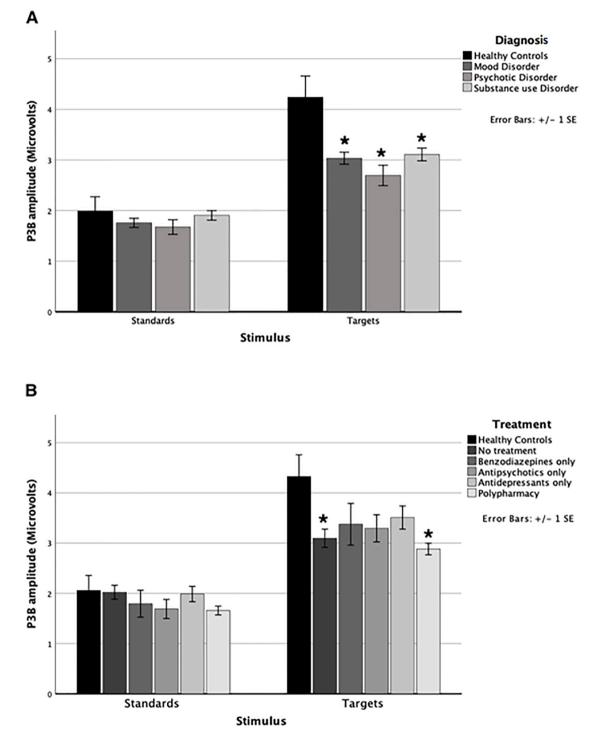

Fig. 2. SA paradigm; P3B amplitudes to standard and target stimuli at electrode Pz, specified per diagnosis and associations with medical treatment. Asterisks in the graphs indicate significantly (p<0.05) higher P3B amplitude to targets for healthy controls than all other patient groups (graph A), as well as significantly higher P3B amplitude to targets for healthy controls than patients without psychotropic medication and patients treated with two or more different types of psychotropic medication (polypharmacy) (graph B).

3.3. MMN paradigm

3.3.1. ERP differences between diagnosis

We found a main effect of Deviant ($F_{1.4,1722}$=428.82; $p<0.001$, η^2=0.43), but no main effect of Group ($F_{3,575}$=2.09; p=0.100, η^2=0.011) nor a Group*Deviant interaction ($F_{4.3,15.8}$=1.31; p=0.262, η^2=0.007). A subsequent split on type of deviant showed that PD patients scored significantly less MMN amplitude to Deviant2 stimuli than either MD (p=0.039) or SUD (p=0.005) patients. MMN amplitude was

also higher in healthy controls relative to PD but this was non-significant (p=0.72). Patients with MD or SUD neither deviated from each other nor from healthy controls ($p>0.40$). No significant group effects in MMN amplitude were found to either deviant 1 or the Beep deviant ($p>0.083$, see also Figure 3A, see also Figure 1B).

Analyses of the P3A amplitude showed a main effect of Deviant ($F_{1.3,282.5}$=39.79; $p<0.001$, η^2=0.065), and a Group*Deviant interaction ($F_{4,50.1}$=2.35; $p=0.05$, η^2=0.012), but no main effect of Group ($F_{3,572}$=2.05; p=0.106, η^2=0.011). A subsequent split on type of deviant
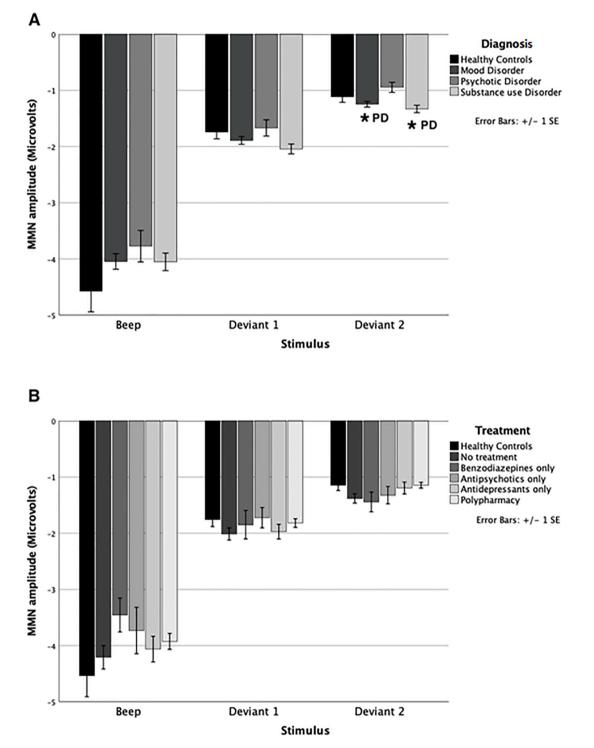

Fig. 3. MMN paradigm; MMN amplitudes to beep, deviant 1 and deviant 2 stimuli at electrode FCz, specified per diagnose and associations with medical treatment. Asterisks in the graphs indicate significantly ($p<0.05$) less MMN amplitude to Deviant 2 stimuli in PD patients compared to either MD or SUD patients (graph A). No significant differences in MMN amplitude were found across the different treatment categories (graph B).

showed that SUD patients scored significantly less P3A amplitude to Beep stimuli than HC (p<0.001) and both MD (p=0.005) and PD (p=0.005) patients, while patients with MD or PD did neither deviate from each other nor from healthy controls (p>0.24). No significant group effects in P3A amplitude were found to either deviant1 or deviant2 (p>0.56) (see Figure 4A, see also Figure 1B).

See supplemental material and figures S2A and S3A for results of MMN and P3A amplitude across subtypes of diagnoses.

3.3.2. ERP differences between medication categories

Similar to the SA paradigm, we compared MMN and P3A amplitude between patients who were treated with one certain category of medication, a combination of categories or no medication at all. This showed no significant associations whatsoever for either MMN (p>0.151; see Figure 3B) or P3A amplitude (p>0.565; see Figure 4B); neither if we split the categories in meaningful subcategories (see supplemental material and figures S2B and S3B).
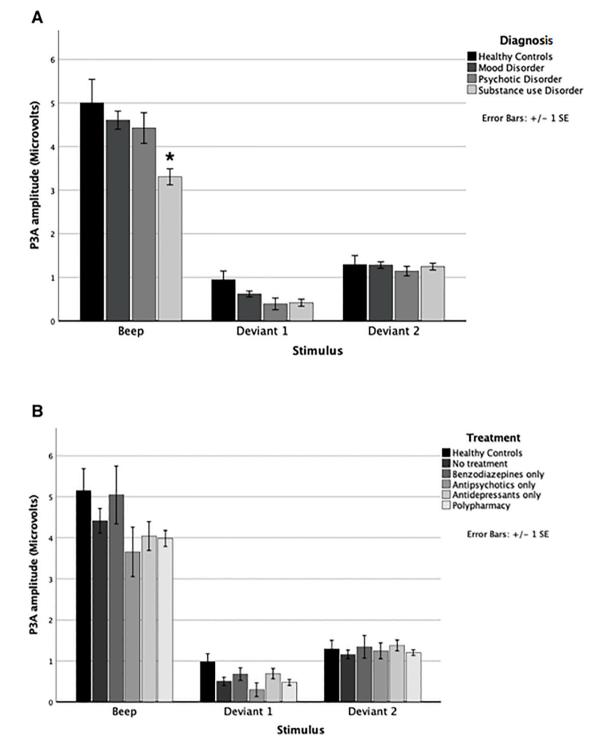

Fig. 4. MMN paradigm; P3A amplitudes to beep, deviant 1 and deviant 2 stimuli at electrode FCz, specified per diagnose and associations with medical treatment. Asterisks in the graphs indicate significantly (p<0.05) less P3A amplitude to Beep stimuli in SUD patients compared to all other groups (graph A). No significant differences in P3A amplitude were found across the different treatment categories (graph B).

3.4. Correlations between psychophysiology and psychometrics

Correlation analyses between symptom severity (using Z-scores calculated from the questionnaire scores) and electrophysiological measures revealed no statistically significant associations between symptom scores and either MMN or P3A amplitudes. However, the P3B amplitude to standard stimuli correlated significantly negatively with symptom severity in SUD (r_S= -0.188, p=0.027). No other significant correlations were found.

4. Discussion

In the current study we explored the impact of psychopathology and treatment on MMN and P3A&B amplitudes in large groups of patients diagnosed with mood disorder (MD), psychotic disorder (PD) and substance use disorder (SUD) and healthy controls. We found significantly lower P3B amplitudes to target stimuli in all major patient groups compared to healthy controls and lower P3A amplitude in SUD patients compared to healthy controls. In addition, we found significantly less MMN amplitude in PD patients compared to either SUD or MD patients (to one of the deviants only). Last, compared to healthy controls, patients treated with polypharmacy or not pharmacologically treated at all had significantly lower P3B amplitudes to targets, while no significant differences in P3A or MMN amplitudes were found over the different treatments.

Compared to healthy controls, patients with schizophrenia (Bramon, Rabe-Hesketh, Sham, Murray, & Frangou, 2004) and depression (Wada et al., 2019) show reduced P3A&B amplitude, while reduced P3B amplitude has also been reported in substance use disorder (Hamidovic & Wang, 2019). In addition, there are numerous studies showing less than usual MMN amplitude in patients with schizophrenia (Umbricht & Krljes, 2005), while contradictory results on MMN are reported in patients with either depression (Lepistö et al., 2004; Qiao et al., 2013) or substance use disorder (e.g. Fein et al., 2004; Marco-Pallarés et al., 2007). However, and as mentioned in the introduction, studies on comparisons of these ERPs between these major psychiatric disorders are lacking. In general, our current results confirm the reports of deficient MMN and P3B amplitude in the above-mentioned patient groups compared to controls, although MMN amplitude was only significantly reduced to Deviant2 stimuli and then only in PD patients compared to MD and SUD patients, not compared to HC; likely, this absence of significance with the controls is caused by power issues, given that the group of controls was rather small. Interestingly, however, we show that the P3A amplitude to the rarest, as well as most strikingly different deviant stimulus, i.e. the "beep", was not only significantly reduced in SUD patients compared to HC, but also to MD and PD patients, whose P3A amplitude to this rare deviant did neither differ significantly from each other nor from HC. The fact that all major patient groups showed reduced P3B amplitude compared to healthy controls, while the patient groups themselves did not differ significantly from each other, indicates that reduced P3B amplitude is likely associated with general psychopathology; at least, in those categories of patients that our subject population consisted of. This appears not solely due to medication given that also patients without medication had significantly reduced P3B amplitude to targets. Given that the P3B amplitude is modulated by noradrenergic and glutamatergic neurotransmission (e.g. Polich, 2007; Oranje et al., 2009; Oranje et al., 2000), this likely indicates that these patients suffer from aberrant activity of these neurotransmitters, whether they are medicated or not. The fact that only PD patients showed reduced MMN amplitude might indicate that MMN deficits are specifically associated with this particular group of patients only; either pointing towards an additional serotonergic deficiency in this group of patients, or a more severe noradrenergic and/or glutamatergic distorted activity, given the neurotransmitters involved in P3B amplitude and MMN, as mentioned above. Similarly, reduced P3A amplitude to rare and striking deviants appeared rather specific for SUD patients, and

might therefore be associated with past or present use of alcohol and/or recreational drugs in that patient group. From a neurotransmitter perspective, this points towards aberrant dopaminergic neurotransmission in this group of patients (Polich, 2007). Speculatively, however, this last finding may also extend to patients with other psychiatric diagnoses who show reduced P3A amplitude, given the higher-than-average use of these types of drugs among psychiatric patients.

Most studies exploring the influence of antipsychotics on MMN and P3A&B deficits in schizophrenia patients report negative associations, i. e. these amplitudes are usually reduced compared to healthy controls, and medication does not ameliorate this (e.g. Kruiper et al., 2019b; Umbricht et al., 1998; Molina et al., 2004; Korostenskaja et al., 2005) with only few exceptions (e.g. Umbricht et al., 1998; Zhou et al., 2013). We therefore also examined the associations with pharmacological treatment (benzodiazepines, antidepressants and antipsychotics) on our amplitude data. We only found that patients who were either not pharmacologically treated at all or treated with polypharmacy had significantly reduced P3B amplitude compared to healthy controls. No other significant associations with medical treatment were found. This result might have been influenced by power issues, given that the significant associations were only found in those treatment categories with the highest numbers of participants. It is therefore difficult to interpret these findings, also in light of the fact that these treatment categories consist of multiple diagnostic categories which, as we know from the results above, exerted their own influence on our electrophysiological measures. Splitting the treatment groups into diagnostic categories was not an option, because the groups simply become too small. Therefore, at best, our data indicates no difference between the type of pharmacological treatment on any of our electrophysiological measures, with the exception that patients treated with polypharmacy appear not better off regarding their deficient selective attention abilities (P3B amplitude) than patients not pharmacologically treated at all.

We found no correlations between electrophysiological measures and symptom severity, besides a significantly negative correlation between the P3B amplitude to the standard stimulus and the severity of symptoms in SUD patients, indicating that the less symptoms these patients have, the more attention they paid towards standard stimuli in the selective attention paradigm. Given that subjects should be more focused on the deviant stimuli in this particular task than to standard stimuli, this may indicate treatment effects. Please note however that his correlation is not that strong, and was not corrected for multiple testing, so it should be treated with the necessary caution.

Our findings contribute to our understanding of ERP differences across diagnostic and medication groups; especially our finding that the P3A amplitude to rare deviants was only reduced in patients with substance use disorder. This may imply that the reduced P3A amplitude as reported in studies on other diagnostic patients is caused by only those patients having a past or present addiction to drugs. After all, recreational drug use is fairly common among psychiatric patients, regardless of diagnostic category. Furthermore, whereas our data indicated that reduced P3B amplitude appears to be associated with general psychopathology, impaired MMN appeared to be specifically associated with psychotic disorders only, relative to MD and SUD. Importantly, given the above-mentioned neurotransmitters that are suggested to be involved in these ERPs, the medical treatment of these patients appears not optimal, and our current results may indicate how to improve treatment for these patients.

An obvious strength of our study is the large group of patients participating in the study as well as the detailed assessment of medication status and symptom severity collected for every individual, allowing for more detailed analyses than several other studies. Limitations of our study were the sex and age differences between our patients and healthy controls. However, wherever these factors covaried significantly in our analyses, they were statistically controlled for. Another limitation is the cross-sectional design of our study, which makes it impossible to theorize on causality between psychopathology, treatment

and electrophysiological parameters of (pre)attentional phenomena. Although there already are some reports on initial treatment naïve and first episode patients in literature, they are only sparse, and usually also included only patients of only one diagnostic category. A last limitation is the fact that all our patients were in-patients, which may limit the generalizability of our results.

In conclusion, we found significantly lower P3B amplitudes in all patient groups compared to healthy controls regardless medical treatment, which adds to the theory that P3B deficits are associated with general psychopathology and not simply due to medical treatment. In contrast, MMN deficits were only found in patients with psychotic disorder, while P3A deficits were only present in patients with substance use disorder, suggesting that these deficits are associated to these specific disorders only.

CRediT authorship contribution statement

JJL, PN and JVH conceived and designed the study idea. BO supervised the research activity planning and execution. LK and BO executed formal analysis. LK wrote the first draft of the manuscript. BO and JJL critically reviewed the manuscript. HM provided detailed pharmacological treatment classifications and BDW managed performing the experiments and data collection. LK, BO and JJL revised the manuscript. All authors contributed to and have approved the final manuscript.

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Declaration of Competing Interest

All authors report no biomedical financial interests or potential conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2022.114637.

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