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Mismatch negativity in schizophrenia spectrum and bipolar disorders: Group and sex differences and associations with symptom severity

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ABSTRACT

Objective: Research increasingly implicates glutamatergic dysfunction in the pathophysiologies of psychotic disorders. Auditory mismatch negativity (MMN) is an electroencephalography (EEG) waveform linked to glutamatergic neurotransmission and is consistently attenuated in schizophrenia (SCZ). MMN consists of two subcomponents, the repetition positivity (RP) and deviant negativity (DN) possibly reflecting different neural mechanisms. However, whether MMN reduction is present across different psychotic disorders, linked to distinct symptom clusters, or related to sex remain to be clarified.

Methods: Four hundred participants including healthy controls (HCs; n = 296) and individuals with SCZ (n = 39), bipolar disorder (BD) BD typeI (n = 35), or BD type II (n = 30) underwent a roving MMN paradigm and clinical evaluation. MMN, RP and DN as well their memory traces were recorded at the FCZ electrode. Analyses of variance and linear regression models were used both transdiagnostically and within clinical groups.

Results: MMN was reduced in SCZ compared to BD ($p = 0.006$, $d = 0.55$) and to HCs ($p < 0.001$, $d = 0.63$). There was a significant group × sex interaction ($p < 0.003$) and the MMN impairment was only detected in males with SCZ. MMN amplitude correlated positively with Positive and Negative Syndrome Scale total score and negatively with Global Assessment of Functioning Scale score. The deviant negativity was impaired in males with SCZ. No group differences in memory trace indices of the MMN, DN, or RP.

Conclusion: MMN was attenuated in SCZ and correlated with greater severity of psychotic symptoms and lower level of functioning. Our results may indicate sex-dependent differences of glutamatergic function in SCZ.

1. Introduction

Schizophrenia spectrum (SCZ) and bipolar disorders (BD) are severe mental illnesses that affect ~1 and ~2 % of the population, respectively (McGrath et al., 2008; Merikangas et al., 2011). These disorders often lead to marked impairments in social and occupational functioning and rank among the leading causes of disability worldwide (Lopez and Murray, 1998). The pathophysiologies of SCZ and BD are likely multifactorial, yet remain incompletely understood (Belmaker, 2004; Freedman, 2003; Misiak et al., 2016). The estimated heritability for SCZ and BD is approximately 60–80 %, which is partly attributable to common risk alleles (Ripke, 2020). Recent large-scale genome-wide association studies (GWAS) have detected SCZ- and BD-associated genetic loci linked to glutamatergic neurotransmission (Devor et al., 2017), consistent with previous preclinical and clinical studies (Catts et al., 2016; Coughlin et al., 2021; Egerton et al., 2020; Kaminski et al.,

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2020; Kaminski et al., 2021; Kumar et al., 2020b; Reddy-Thootkur et al., 2022). Impaired glutamatergic neurotransmission has therefore emerged as one of the leading candidate mechanisms shared between SCZ and BD (Dienel et al., 2020; Egerton et al., 2020; Garrido et al., 2009; Huang et al., 2020).

Auditory mismatch negativity (MMN) is an event-related brain response sensitive to deviations within a sequence of repetitive auditory stimuli that can be reliably assessed using electroencephalography (EEG) (Avissar and Javitt, 2018; Garrido et al., 2008). The MMN is commonly computed as the difference wave between the event-related potentials (ERPs) elicited by frequent standard and rare deviant sounds (Garrido et al., 2009). MMN is widely assumed to reflect a pre-attentive process that occurs automatically as a cortical correlate of prediction error, serving to update and modify internal representations of the external environment (Garrido et al., 2009; Harms et al., 2021). MMN attenuation has been linked to hypofunction of the glutamatergic *N*-methyl-D-aspartate (NMDA)–receptor (Featherstone et al., 2015; Harms et al., 2021; Javitt et al., 1996; Rosburg and Kreitschmann-Andermahr, 2016), reduced activity of inhibitory interneurons (Javitt et al., 2018; Ross and Hamm, 2020), and subsequent aberrant neurotransmission of glutamatergic pyramidal cells (Huang et al., 2020; Limongi et al., 2020; McCutcheon et al., 2020). Reduced MMN amplitude is one of the most consistently reported biological abnormalities in SCZ (Erickson et al., 2016; Umbricht and Krljes, 2005), and is associated with occupational disability (Hamilton et al., 2018; Kaur et al., 2013; Wynn et al., 2010), reduced global functioning (Higgins et al., 2021; Kim et al., 2014; Koshiyama et al., 2018; Light and Braff, 2005b), and possibly decreased cortical volumes in temporal and frontal regions in SCZ (Curtis et al., 2021; Rasser et al., 2011; Salisbury et al., 2020). MMN deficits may develop early in the disease trajectory (Atkinson et al., 2012; Bodatsch et al., 2011; Erickson et al., 2016; Hamilton et al., 2022) and were linked to cognitive deficits in SCZ (Baldeweg et al., 2004; Higuchi et al., 2013; Javitt et al., 1995; Li et al., 2021; Naatanen et al., 2014). Some studies reported significant relationships between MMN and negative (Catts et al., 1995; Light et al., 2015; Naatanen and Kahkonen, 2009) and positive (Fisher et al., 2011; Fisher et al., 2008, 2012; Francis et al., 2020; Kargel et al., 2014; Light et al., 2015; McCleery et al., 2018; Sun et al., 2020) symptoms, yet a recent meta-analysis did not find evidence for these associations (Erickson et al., 2017).

Little is known regarding the effects of sex on MMN in the psychoses despite emerging evidence for differences in the glutamatergic system between males and females with SCZ (Wickens et al., 2018). In animal models, female sex hormones modulate NMDAR inhibition (Gogos et al., 2012; Hill, 2016; Huang et al., 2017), and attenuate auditory sensory gating impairments (Thwaites et al., 2014; Xia et al., 2021). In the anterior cingulate cortex, which is involved in MMN generation (Koshiyama et al., 2021; Oknina et al., 2005), increased levels of glutamate metabolites and reduced expression of glutamate regulating enzymes were found in males with SCZ when compared to female patients (Martins-de-Souza et al., 2010; Tayoshi et al., 2009). Furthermore, increased density of NMDA receptors has been found in females with SCZ (Coyle et al., 2002; Wickens et al., 2018) and increased expression of cortical GABAergic interneurons was detected in female rodents (Du et al., 2018; Wu et al., 2014), relative to males. Moreover, there are established sex differences in key clinical traits in the psychotic illnesses, e.g., earlier age of psychosis onset (Fernando et al., 2020; Hafner, 2019), greater functional decline (Seeman, 2021; Zorkina et al., 2021), and greater levels of neuroanatomic abnormalities (Goldstein et al., 2002; Mendrek and Mancini-Marie, 2016; Nopoulos et al., 1997; Yang et al., 2021), in males than in females.

MMN is less well-studied in BD than in SCZ (Kim et al., 2020; Kim and Park, 2020; Shimano et al., 2014). Several previous studies found no significant MMN difference between individuals with BD and healthy controls (HC) (Baldeweg and Hirsch, 2015; Catts et al., 1995; Hall et al., 2007), yet these had modest sample sizes. Recent meta-analyses suggest that MMN is impaired in BD with a small to intermediate effect size (Hermens et al., 2018; Raggi et al., 2021), but there are few studies that have examined MMN in subgroups of BD. Only two previous studies with moderate sample sizes compared MMN between BD types I and II (Jahshan et al., 2012; Kim and Park, 2020) and did not detect significant group differences. Some evidence indicates that the MMN impairment in BD is associated with the presence of psychosis (Kaur et al., 2012a; Raggi et al., 2021) and one recent study observed attenuated MMN across diagnoses in a mixed cohort of psychotic disorders, thus suggesting that MMN impairment may reflect a transdiagnostic susceptibility to psychosis (Donaldson et al., 2020). However, only one previous study assessed the effects of a history of psychosis on MMN in BD and found no significant MMN difference between those with and without psychosis history (Baldeweg and Hirsch, 2015).

In the present study, we employed a roving MMN paradigm with continuously changing standard stimuli in a Scandinavian sample of clinically well-characterized patients with SCZ, BD types I and II, and HCs. The roving paradigm also allows for the quantification of the repetition positivity (RP) and the deviant negativity (DN); these are MMN components which strengthens with increasing number of standard repetitions in HCs, thereby yielding a "memory trace" (Baldeweg, 2006; Baldeweg et al., 2004; Haenschel et al., 2005; McCleery et al., 2019). There are only a few studies of RP and DN memory traces in psychosis and some, but not all, of these detected impairments in patients with SCZ, possibly reflecting deficits in predictive coding and predictive error signaling (Baldeweg and Hirsch, 2015; Baldeweg et al., 2004; Fryer et al., 2020; McCleery et al., 2019). Here, we first hypothesized that MMN, RP, and DN would be reduced in SCZ and in BD patients with a history of psychosis. Second, we tested the hypothesis that these impairments would be greater in male than female patients. Finally, we explored the relationships between MMN and central clinical features across groups and within the sexes.

2. Materials and methods

2.1. Participants

The current work was based on the Thematically Organized Psychosis (TOP) study, a Norwegian multi-site study focusing on underpinnings and clinical characteristics of SCZ and BD. The patients were recruited from psychiatric hospitals and outpatient clinics in the greater Oslo area. All participants were between 18 and 65 years and met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), criteria for a SCZ spectrum disorder (schizophrenia, schizoaffective disorder, schizophreniform disorder), BD type I or BD type II. There was a prerequisite that the patient had capacity for informed consent. Exclusion criteria for the patients were IQ < 70, neurological illness, autism spectrum disorder, brain injury or history of severe head trauma with loss of consciousness or other significant medical illness affecting brain function. Prior or current substance abuse was not an exclusion criterion. Alcohol and drug consumption were assessed with the Alcohol Use Disorders Identification Test (AUDIT) (World Health Organization et al., 2001) and the Drug Use Disorders Identification Test (DUDIT) (Berman et al., 2002), and patterns of use were recorded. HCs ($n = 403$) were recruited through national records, social media and advertisements in a regional newspaper in the same catchment area. Controls underwent the Primary Care Evaluation of Mental Disorders (PRIME-MD) (Spitzer et al., 1999). The exclusion criteria for HCs were the same as for the patients and also included the following: a) a history of SCZ, BD, or major depressive disorder (MDD) and b) having a first degree relative with SCZ, BD, or MDD.

2.2. Clinical assessments

All patients were examined by a trained clinician with clinical interviews for the DSM-IV (SCID-I) (Association, 2013), Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and Inventory of

Table 1
Demographic and clinical characteristics of patients and trimmed control sample.

	Schizophrenia (n = 39)	Bipolar type 1 (n = 35)	Bipolar type 2 (n = 30)	Controls trimmed (n = 296)	p-value
Age (years), (mean, sd)	33.6 (10.3)	36.4 (12.5)	29.7 (10.8)	40.7 (11.2)	<.001
Female (n, %)	18 (46.1 %)	24 (68.6 %)	17 (56.7 %)	157 (53.0 %)	.25
Years of education (years) (mean, sd)	14.8 (3.2)[a]	16.4 (3.0)	15.2 (3.1)	14.9 (2.1)	.18
Currently gainfully employed or studying (n, %)	8/35 (22.9 %)[b]	17/32 (53.1 %)[c]	21/29 (72.4 %)[d]	–	<.001
Lifetime psychosis (n, %)	39 (100 %)	21 (60.0 %)	6 (20.0 %)	–	<.001
Lifetime number of affective episodes (mean, sd)	2.1 (2.5)	11.1 (12.2)	10.2 (9.2)	–	<.001
Lifetime number of psychotic episodes (mean, sd)	3.4 (4,9)	1.4 (1.8)	0,4 (0,9)	–	.21
Age of disease onset (mean, sd)	24.7 (10,3)	22.2 (9,0)	16.7 (4,9)	–	<.001
Duration of illness (years, mean, sd)	11.1 (7.7)	13.7 (11.8)	13.2 (9.8)	–	.012
GAF-S (mean, sd)	52.9 (12.3)	63.3 (10.8)	60.9 (9.8)	–	.002
GAF-F (mean, sd)	52.4 (14.5)	62.2 (12.6)	59.8 (11.0)	–	.04
IQ (mean, sd)	104.1 (15.0)[b]	109.6 (13.6)[b]	114.5 (13.1)[d]	116.0 (9.8)[e]	<.001
PANSS- total (mean,sd)	59.0 (15.4)	43.8 (7.2)	45.5 (0.2)	–	.003
Positive factor	8.9 (3.8)	5.3 (1.9)	5.3 (2.3)	–	<.001
Negative factor	11.9 (5.4)	8.3 (3.1)	8.9 (3.1)	–	.007
Disorganized factor	5.0 - (2.1)	3.7 (1.1)	3.9 (1.8)	–	.003
Excited factor	3.9 (1.2)	3.5 (0.8)	3.3 (0.7)	–	.38
Depressive factor	7.1 (2.8)	8.0 (2.9)	8.8 (2.8)	–	.14
IDS (mean, sd)	14.7 (8.5)	12.9 (12.8)	20.3 (11.9)	–	.01
MADRS (mean, sd)	10.9 (5.9)[e]	11.2 (8.3)[b]	16.0 (10.7)[d]	1.6 (2.5)[g]	<.001
YMRS (mean, sd)	2.7 (3,6)[f]	3.7 (5.6)[b]	4.6 (4.6)[d]	0.8 (1.4)[g]	<.001
History of alcohol use disorder[h] (n, %)	8/39 (21 %)	2/35 (6 %)	3/30 (10 %)	0/296 (0 %)	<.001
History of substance use disorder[i] (n, %)	10/39 (26 %)	3/35 (9 %)	4/30 (13 %)	0/296 (0 %)	<.001
Daily nicotine use (n, %)	23/39 (59 %)	14/35 (40 %)	15/15 (50 %)		.27
Units of alcohol last 2 weeks (mean, sd)	7,1 (15.5)	5.6 (8.2)	9.8 (18.2)	7,6 (7,2)	.48
Intake of illicit substances last 2 weeks (n, %)	2/39 (5 %)	2/35 (6 %)	4/30 (13 %)	–	.45
AUDIT (mean, sd)	6.1 (5.8),	5.9 (6.1),	8.4 (5.4)	4.9 (3.1)	<.001
DUDIT (mean, sd)	4.3 (8.2), Range (0–37)	2.4 (5.0), Range (0–20)	4.2 (7.9), Range (0–29)	0.3 (1.2) Range (0–12)	<.001
Number of psychotropic drugs used (mean, sd)	1.3 (0.9)	1.5 (1.3)	1.2 (1.0)	0 (0 %)	.733

Abbreviations: GAF-S: global assessment of functioning-symptom scale; GAF-F global assessment of functioning- symptom scale; PANSS: the Positive and Negative Syndrome Scale; IDS: Inventory of Depressive Symptoms; MADRS: Montgomery-Asberg Depression Rating Scale; YMRS: Young Mania Rating Scale.
Note: Standard deviations are put in brackets if not otherwise specified. Duration of illness and age of onset is denoted in years.
Missing data: [a] n = 2, [b] n = 4, [c] n = 3, [d] n = 1, [e] n = 25, [f] n = 7, [g] n = 51.
[h] Per DSM-IV criteria for alcohol abuse and dependency, remitted cases included.
[i] Per DSM-IV criteria for drug abuse and dependency, all substances, remitted cases included.

Depressive Symptoms (IDS) (Rush et al., 1996). Mood was further assessed on the day of the EEG recording using the Montgomery-Åsberg depression rating scale (MADRS) (Montgomery and Asberg, 1979) and Young Mania Rating Scale (YMRS) (Young et al., 1978). Age of onset, lifetime number of psychotic and affective symptoms and level of functioning, as assessed by the Global Assessment of Functioning (GAF-F/S, split version) (Pedersen et al., 2007), were obtained. The patient sample included individuals with SCZ (n = 39, i.e., 30 with schizophrenia, 7 with schizoaffective, and 2 with schizophreniform disorder) and BD (n = 65, i.e., 35 with BD type I and 30 with BD type II; Table 1).

2.3. EEG acquisition and preprocessing

Scalp EEG data was amplified (−3 dB at 417 Hz low-pass, DC-coupled) and digitized (2048 Hz) from 72 Ag/AgCl active electrodes, including 64 active channels positioned according to the international 10–5 system, using a Biosemi Active-Two amplifier (BioSemi, Amsterdam, The Netherlands). All electrode offsets were kept below ±30 μV. The offline analyses were conducted in Matlab 2017a (Mathworks Inc., Natick, MA) using EEGLAB (S, 2004) and in-house scripts. The data was first low-pass filtered at 40 Hz, then downsampled to 512 Hz, subjected to a high-pass filter at 0.5 Hz, and re-referenced to the average of left and right mastoids. Line noise and bad channels were removed using the PREP pipeline (Bigdely-Shamlo et al., 2015) and affected channels were interpolated using a robust average reference. The mean number of interpolated channels was 4.5 (standard deviation (SD) 3.1, range 1–15). Epochs were then extracted from −100 ms to 400 ms relative to stimulus onset. Independent component analysis (ICA) was conducted using binica and independent components representing artefacts were identified using ICLabel (Pion-Tonachini et al., 2019). Components with label probabilities <30 % brain and >50 % non-brain were removed, thus resulting in the removal of 22.5 components on average (SD 6.2, range 5–59). Epochs were then baseline-corrected by subtracting the mean amplitude from −50 ms to 0 ms relative to stimulus onset and epochs with amplitudes exceeding ±100 mA were rejected.

2.4. Mismatch negativity paradigm

The participants were seated in a comfortable chair during the EEG data collection. Hearing threshold was tested binaurally using a pure sinusoidal 1000 Hz tone and participants with a threshold of >40 dB

Table 2.
Gender differences in clinical characteristics by group.

	Schizophrenia (n = 39)			Bipolar disorder (n = 65)		
	Male (n = 21)	Female (n = 18)	p-value	Male (n = 24)	Female (n = 41)	p-value
Age (years, mean, sd)	32.6 (10.3)	34.8 (10.5)	.51	33.5 (13.3)	33.2 (11.5)	.94
Years of education (mean, sd)	14.8 (3.5)[a]	14.7 (3.0)[a]	.81	15.7 (3.3)	16.0 (2.9)	.48
Currently gainfully employed or studying (n,%)	6/19 (30 %)[b]	2/17 (11.8 %)[b]	.21	17/22 (77.2 %)[b]	21/39 (53.8 %)[b]	.09
Number of affective episodes (mean, sd)	1.3 (1.6)	2.9 (3.0)	.07	10.5 (10.1)	10.8 (11.3)	.92
Number of psychotic episodes (mean, sd)	3.5 (3.8)	5.9 (13.2)	.49	0.8 (1.2)	1.0 (1.7)	.45
Age of disease onset (mean, sd)	23.5 (7.3)	25.6 (11.7)	.51	18.0 (5.2)	20.6 (8.6)	.13
Duration of illness (years, mean, sd)	9.1 (8.1)	9.2 (6.3)	.97	15.6 (14.0)	12.6 (9.2)	.36
GAF-S (mean, sd)	54.1 (13.6)	52.0 (9.9)	.58	60.8 (9.0)	63.4 (10.8)	.30
GAF-F (mean, sd)	55.2 (17.0)	50.1 (11.3)	.27	61.9 (11.9)	61.7 (12.2)	.95
IQ (mean, sd)	101.8 (13.9)	109.1 (15.7)	.18	115.8 (11.0)	111.9 (12.4)	.22
PANSS- total (mean, sd)	55.9 (15.9)	57.3 (12.9)	.75	45.1 (8.4)	44.0 (9.8)	.65
Positive factor	8.4 (3.9)	9.6 (3.8)	.34	5.4 (1.8)	5.2 (2.2)	.76
Negative factor	12.3 (6.2)	11.5 (4.5)	.65	9.3 (3.5)	8.1 (2.7)	.16
Disorganized-concrete factor	5.2 (2.1)	4.8 (2.0)	.49	4.0 (1.6)	3.7 (1.3)	.37
Excited factor	3.9 (1.3)	3.9 (1.1)	.97	3.5 (0.7)	3.4 (0.7)	.72
Depressive factor	6.5 (3.0)	7.8 (2.3)	.14	8.0 (2.7)	8.6 (2.9)	.37
IDS (mean, sd)	13.3 (9.1)	16.4 (7.7)	.28	15.4 (12.7)	16.8 (13.0)	.68
MADRS (mean, sd)	10.5 (6.0)[c]	11.4 (5.9)[b]	.69	13.1 (9.6)[b]	13.6 (9.9)[d]	.96
YMRS (mean, sd)	2.5 (3.3)	2.9 (3.9)	.73	4.5 (4.5)[a]	3.7 (5.3)	.50
History of alcohol abuse[e] (n, %)	3/21 (14 %)	5/18 (28 %)	.30	2/24 (8 %)	3/41(7 %)	.82
History of drug abuse[f] (n, %)	5/21 (24 %)	5/18 (28 %)	.78	4/24 (17 %)	3/41 (7 %)	.24
Daily intake of nicotine (n, %)	13/21 (61 %)	10/18 (56 %)	.68	10/24 (42 %)	19/22 (46 %)	.71
Alcohol units last 2 weeks (mean, sd)	7.0 (11.2)	7.2 (19.5)	.97	12.0 (19.7)	4.8 (7.4)	.040
Intake of illicit substances last 2 weeks (n, %)	1/21 (5 %)	1/18 (6 %)	.36	5/24 (21 %)	1/40 (3 %)	.046
AUDIT (mean, sd)	5.7 (4.9)	6.5 (6.8)	.67	7.6 (5.7)	6.8 (6.2)	.59
DUDIT (mean, sd)	4.8 (8.6), Range (0–37)	3,8 (7.8), Range (0–26)	.73	4.0 (6.0), Range (0–17)	2.8 (6.8) Range (0–29)	.46
Total psychotropic drugs used (mean, sd)	1.6 (1.0)	1.1 (0.8)	.07	1.2 (1.1)	1.5 (1.3)	.27
DDD-Antipsychotics (mean, sd)	0.96 (0.59)	1.07 (0.58)	.63	0.85 (0.32)	0.82 (0.65)	.91

Abbreviations: GAF-S: global assessment of functioning-symptom scale; GAF-F global assessment of functioning- symptom scale; PANSS: the Positive and Negative Syndrome Scale; IDS: Inventory of Depressive Symptoms; MADRS: Montgomery-Asberg Depression Rating Scale; YMRS: Young Mania Rating Scale. DDD: defined daily dose.
Note: Standard deviations are put in brackets. Age of disease onset and duration of illness is measured in years.
Missing data: [a] n = 1, [b] Missing data: n = 2, [c] Missing data: n = 5, [d] Missing data: n = 3.
[e] Per DSM-IV criteria for alcohol abuse and dependency, remitted cases included.
[f] Per DSM-IV criteria for alcohol abuse and dependency, all substances, remitted cases included.

were excluded. MMN was obtained by a roving paradigm, scripted and presented using PsychToolbox in Matlab (Brainard, 1997) while the participants were reading a magazine to divert attention from the presented stimuli. Pure sinusoidal tones were presented binaurally (80 dB, 5 ms rise and fall times) by earphones (ER-2, Etymotic Research, Inc., Elk Grove Village, IL, USA) with a fixed stimulus onset asynchrony of 400 ms. In the roving paradigm, trains of identical standard auditory stimuli with regards to pitch and duration were presented in a pseudo-random fashion with 2, 6, or 18 repetitions alternating with a new train of stimuli with different physical properties, thus resulting in the first tone of a new train acting as a deviant stimulus relative to last tone of the previous stimulus train, as described by Baldeweg and colleagues (Baldeweg et al., 2004). The pitch of the employed 24 tones ranged from 700 to 1250 Hz, and the duration of the tones was either 50 or 100 ms. For each new tone sequence, both the frequency and the duration of the tones changed, thus making the first tone of a new sequence a "double deviant", accounting for 11.5 % of the total number of stimuli. The roving paradigm has the advantage that standards and deviants have identical physical properties and thereby corrects for the possibility that recruitment of different neuronal populations by the standards and deviants may confound the prediction error signal that is believed to account for the MMN.

ERP waves from the FCZ electrode were calculated for both the deviant and the immediately preceding standard stimulus by extracting the mean amplitudes in the 100 to 200 ms post-stimulus interval. MMN was then estimated by subtracting the amplitude of the deviant waveform from that of the waveform elicited by the preceding standard stimulus. The roving paradigm allows for the extraction of separate mismatch responses to the deviants presented after 2, 6, or 18 standard repetitions, hereafter referred to as 2-MMN, 6-MMN, and 18-MMN, respectively, and the MMN memory trace, (MMN_{MT}), here defined as the 18-MMN minus the 2-MMN. The mean numbers of trials for 2-MMN, 6-MMN, and 18-MMN were 84.9 (SD 4.1, range 49–89), 81.1 (SD 5.8, range 46–88), and 83.2 (SD 5.6, range 57–90), respectively. A grand average MMN was calculated by averaging the 2-, 6-, and 18-MMNs. 2-, 6-, and 18-RPs were calculated as the mean amplitudes for the 2nd, 6th and 18th standard repetition in the 100 to 200 ms post-stimulus interval, a grand average RP was estimated by averaging the 2-, 6-, and 18-RPs, and an RP memory trace index (RP_{MT}) was calculated by subtracting the 2-RP from the 18-RP. 2-, 6-, and 18-DNs were calculated as the mean amplitudes for deviants immediately succeeding the 2nd, 6th, and 18th standard repetition in the 100 to 200 ms post-stimulus interval, a grand average DN was estimated by averaging the 2-, 6-, and 18-DNs, and a DN memory trace index (DN_{MT}) was calculated by subtracting the 2-DN from the 18-DN.

During data collection, we discovered an error in the Matlab-based script, which resulted in the presentation of a 1050 Hz 50 ms tone instead of a 100 ms tone. This affected 6 of the 91 2-repetitions trials, 10 of the 88 6-repetitions trials, and 10 of the 90 18-repetitions trials, in 229 of the participants. These trials were excluded from the data of these individuals. Although it was highly unlikely that this error would affect results, the main group comparisons were also run with separate

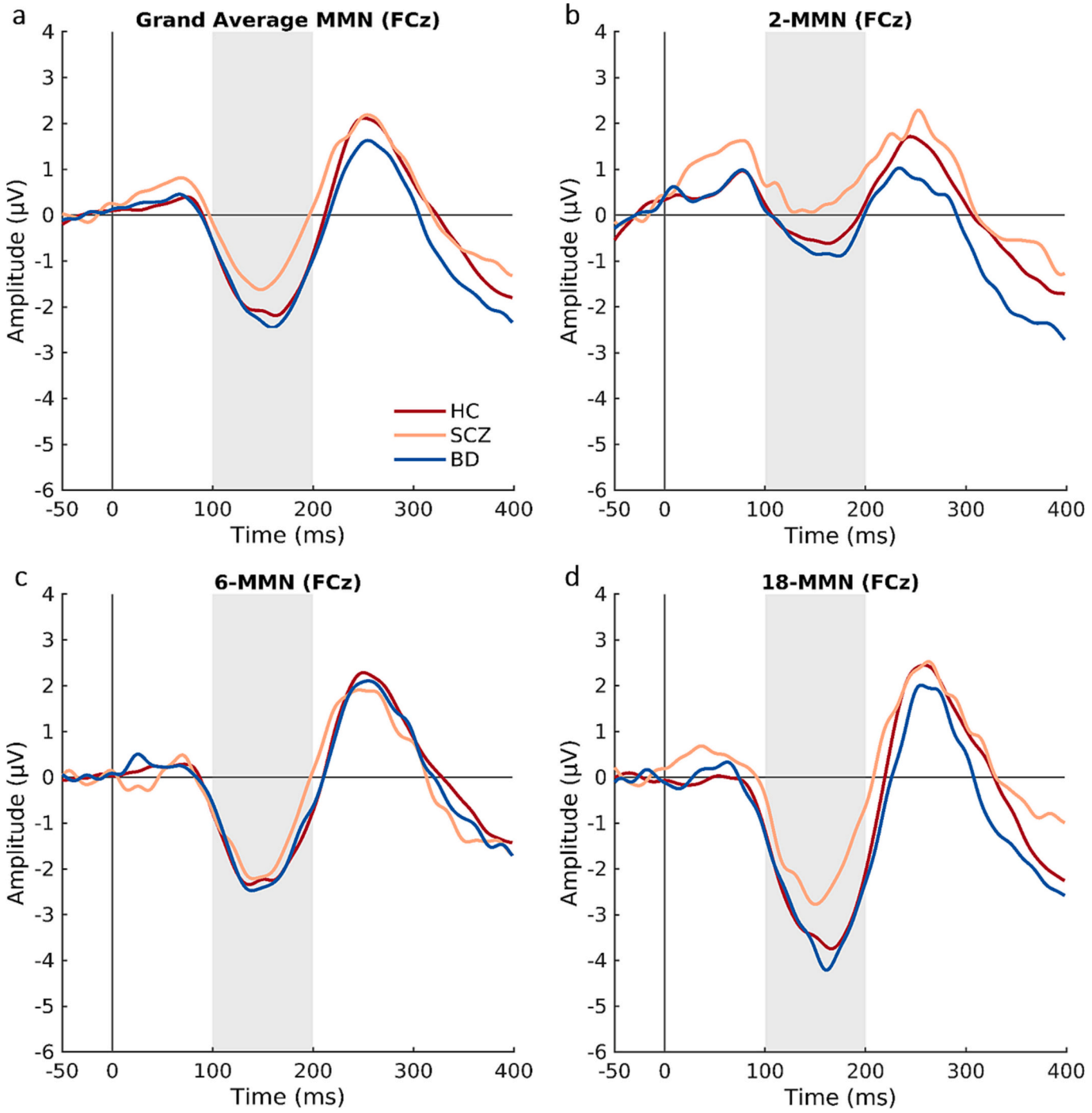

Fig. 1. Mismatch negativity (MMN) in healthy controls (HC) and individuals with schizophrenia (SCZ) or bipolar disorder (BD). a) illustrates the grand average MMN across 2, 6 and 18 repetitions of standard auditory stimuli, whereas b), c), and d) show MMN after 2, 6 and 18 repetitions, respectively.

analyses for participants with (n = 229) and without (n = 171) less trials.

2.5. Statistical analyses

Statistical analysis was performed in R version 3.6.1 (R Core Team, 2020). Clinical and demographic variables were assessed using one way analysis of variance (ANOVA) for continuous variables and the chi-squared test for categorical variables. Gender differences in clinical and demographic variables were examined within each diagnostic group using independent sample *t*-tests. The mean age of the HCs was significantly greater than the patient groups. We therefore computed age-adjusted Z scores modeled by the HC-group (n = 403) for grand average MMN, MMN_{MT}, grand average RP, RP_{MT}, grand average DN, and DN_{MT}, as conducted in prior MMN research (Fryer et al., 2020; Hamilton et al., 2022; Perez et al., 2014), and these were used in the statistical analyses. This use of age-adjusted Z scores removes effects of normal aging and maturation, as modeled in the HC group, while retaining potential pathological aging- and maturation-effects in the data from patients. Next, we excluded HCs older than the oldest patient (>62 years) and the resulting control sample (n = 296) was used in the statistical analyses.

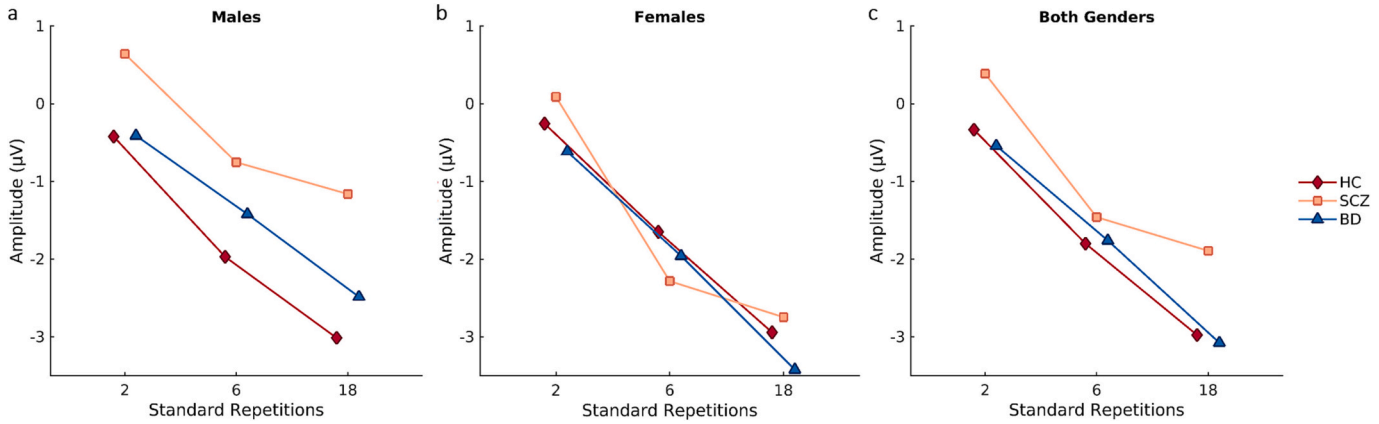

Fig. 2. The figure illustrates increasing mismatch negativity (MMN) amplitude with larger number of repetitions of standard auditory stimuli (2, 6, and 18 repetitions) in healthy controls (HC) and individuals with schizophrenia (SCZ) or bipolar disorder (BD) in a) males, b) females, c) the sexes combined.

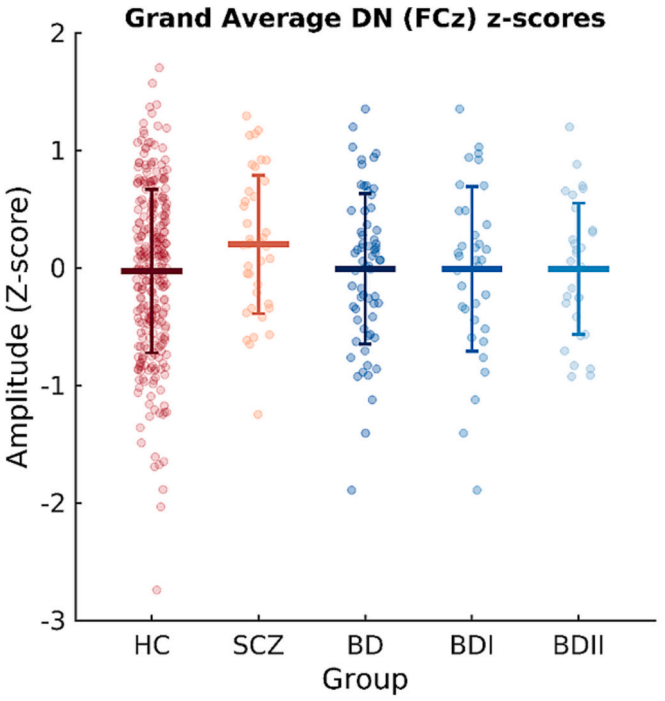

Fig. 3. Scatter plots indicating grand average deviant negativity (DN) across 2, 6 and 18 repetitions of standard auditory stimuli in individuals with schizophrenia (SCZ), bipolar disorder type I (BDI) and type 2 (BDII), and in healthy controls (HC). The horizontal line indicate the mean and the whiskers reflect the 1.5 interquartile range.

Group differences in the MMN, DN, and RP variables were assessed using two-way analyses of variance (ANOVA) with group and sex as the between-subjects factors and with Tukey HSD post-hoc analyses. Age was used as covariate in all analyses. Analyses were run for the combined BD sample, for BD types I and II separately, and for individuals with BD with and without a lifetime history of psychosis. All dependent variables were assessed for normality and homogeneity of variance. Repeated measures ANCOVAs were then run to assess the effects of number of standard repetitions on MMN, DN, and RP. Mauchly's test was run to evaluate whether the assumption of sphericity was violated and coefficients were Greenhouse-Geisser corrected when appropriate.

The relationships between MMN and clinical characteristics were explored across and within the clinical groups, adjusting for age, sex and - in the transdiagnostic analyses - for diagnosis. The analyses were then conducted for each sex separately. Linear regressions were performed for MMN and illness duration, age of onset of first clinical episode, defined daily dose (DDD) of antipsychotics, and lifetime number of psychotic and affective episodes. Linear regressions with age and sex included in the models were used to investigate the relationship between MMN and GAF-S/F and PANSS total and subscores, according to the Wallwork-Fortgang five-factor model (Wallwork et al., 2012).

3. Results

3.1. Demographics and clinical variables

The demographic and clinical variables are detailed in Table 1. The controls were significantly older than the patients and the SCZ group had lower GAF-F and higher PANSS total score than the BD group. The individuals with SCZ had significantly lower IQ scores than the participants with BD and HCs (Table 1), in a magnitude consistent with the published literature (Flaaten et al., 2022; Heinrichs and Zakzanis, 1998). There were no significant differences in clinical characteristics between females and males within the SCZ or the BD group (Table 2).

3.2. Group comparisons for MMN, RP, and DN

3.2.1. Schizophrenia vs. bipolar disorder vs. healthy controls

For grand average MMN (Fig. 1a), we observed a significant effect of group ($F(2, 394) = 6.85$, $p = 0.001$) and a significant group × sex interaction ($F(2, 394) = 6.27$, $p = 0.002$). Post-hoc comparisons showed a significant reduction in MMN in SCZ compared to HCs ($p < 0.001$, Cohen's $d = 0.63$, 95 % CI 0.29–0.97) and to BD ($p = 0.007$, Cohen's $d = 0.55$, 95 % CI 0.15–0.97). There was no significant difference between BD and HCs ($p = 1.00$). Furthermore, post-hoc analyses showed that grand average MMN was impaired in males with SCZ relative to male HCs ($p < 0.001$, Cohen's $d = 1.16$, 95 % CI 0.81–1.50) and male BD ($p < 0.023$; Cohen's $d = 0.74$, 95 % CI 0.33–1.15), yet there were no significant MMN differences between female patients and female controls (all $p > 0.46$). There was a significant effect of repetitions (2 vs. 6 vs. 18) on MMN amplitude ($F(2, 788) = 50.71$, $p < 0.001$), yet no significant group × repetitions or sex × repetitions interaction (all $p > 0.10$; Fig. 2). There was no significant effect of group on MMN_{MT} ($F(2, 397) = 0.51$, $p = 0.61$).

There was no significant effect of group on grand average RP ($F(3, 393) = 1.96$, $p = 0.14$). We found a significant effect of repetitions on RP ($F(1.876, 742.821) = 56.838$, $p < 0.01$), yet no significant group × repetitions or sex × repetitions interaction (all $p > 0.58$). There was no significant effect of group on RP_{MT} ($F(2, 393) = 0.237$, $p = 0.78$).

For grand average DN (Fig. 3), there was no significant effect of group ($F(2, 394) = 2.03$, $p = 0.13$), yet there was a significant group ×

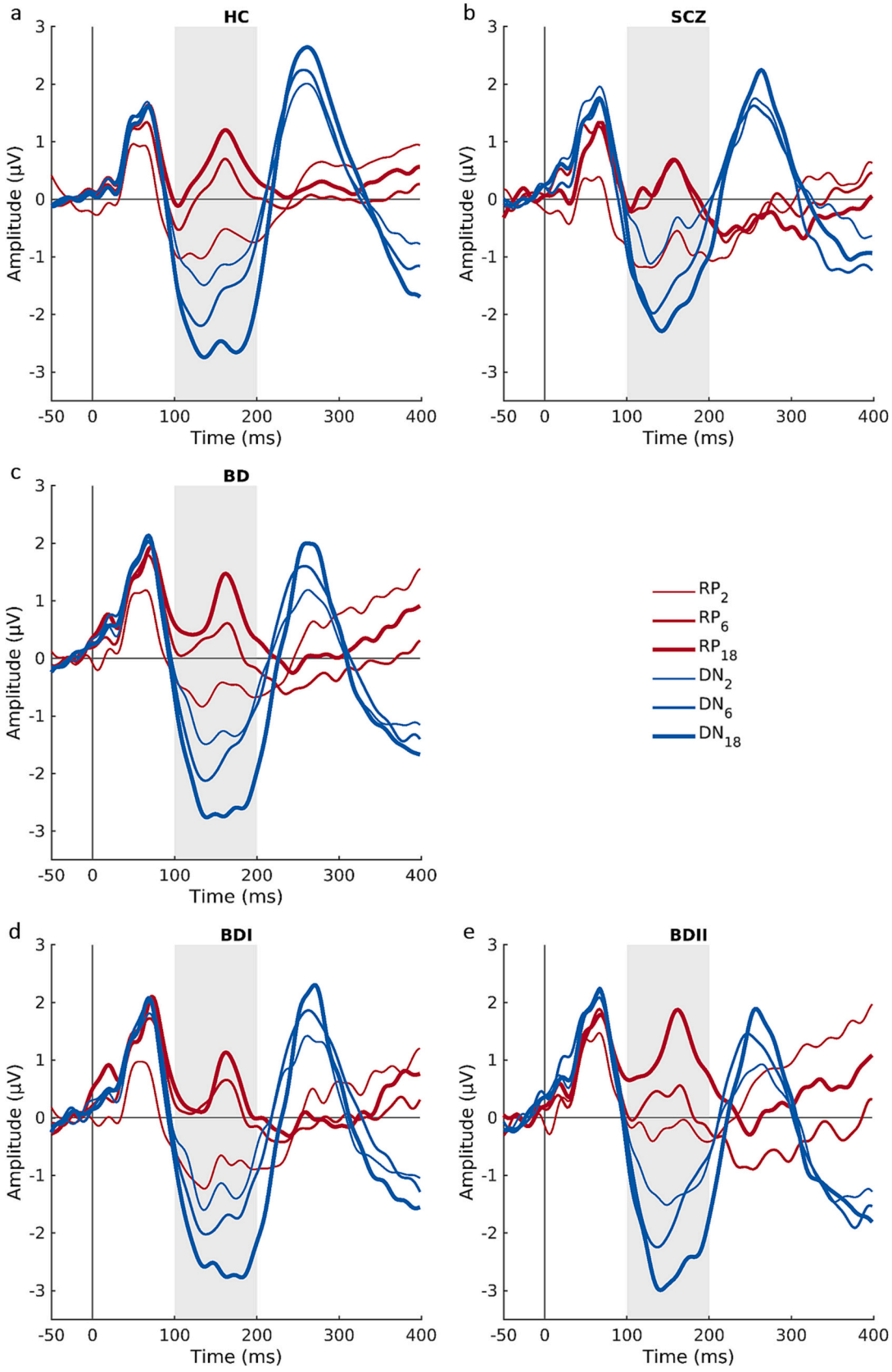

Fig. 4. Event related potentials (ERP) of repetition positivity (RP) and deviant negativity (DN) after 2, 6 and 18 standard repetitions in a) healthy controls (HC), b) individuals with schizophrenia (SCZ), c) individuals with bipolar disorder (BD) types I and II combined, d) individuals with BD type I (BDI), and e) individuals with BD type II (BDII).

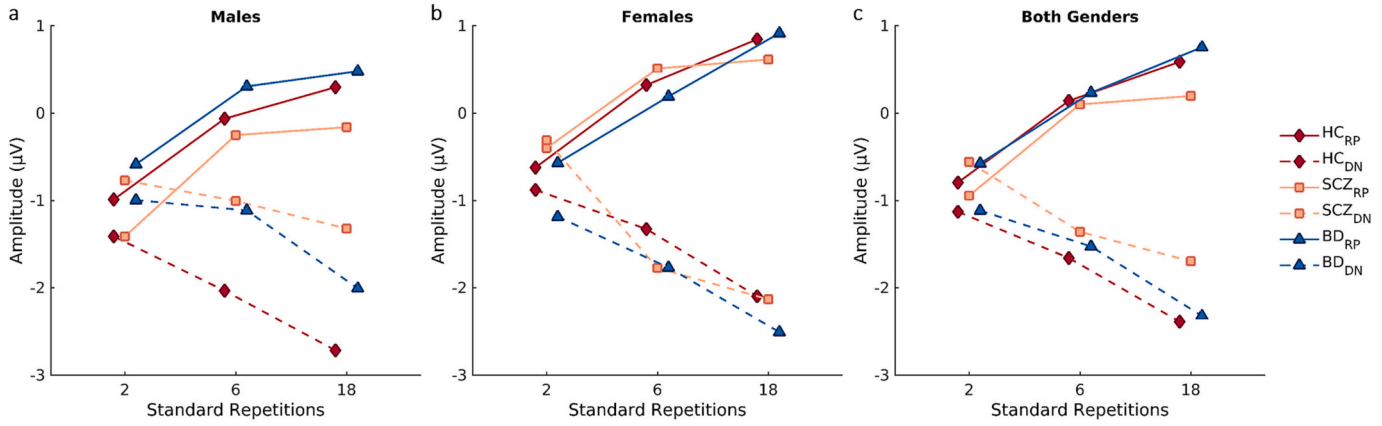

Fig. 5. The figure illustrates amplitude development of repetition positivity (RP) and deviant negativity (DN) with larger number of repetitions of standard auditory stimuli (i.e., 2, 6, and 18 repetitions) in healthy controls (HC) and individuals with schizophrenia (SCZ) or bipolar disorder (BD) in a) males, b) females, and c) the two sexes combined.

sex interaction ($F(2, 395) = 4.80$, $p = 0.009$). Here, post-hoc tests showed impaired DN in males with SCZ vs. control males ($p = 0.012$; Cohen's $d = 0.66$, 95 % CI 0.31–0.99), whereas no group differences were found in the female group (all $p > 0.46$). There was a significant effect of repetitions on DN ($F(1.949, 771.884) = 42.87$, $p < 0.001$), but no significant group × repetition effect ($p = 0.74$; Figs. 4, 5). For DN_{MT}, there was no significant effect of group ($F(2, 394) = 0.32$, $p = 0.87$), yet a significant group × sex interaction ($F(2, 394) = 4.05$, $p = 0.018$); here, post-hoc tests showed a trend towards reduced DN_{MT} in SCZ vs. HC in the male group only ($p = 0.064$).

The main analyses were then rerun for participants with less trials ($n = 229$) and for the other participants ($n = 171$) separately. In both subsamples, there was a significant effect of group on grand average MMN with significant reductions in SCZ and there were significantly reduced grand average MMN and grand average DN in males with SZC relative to male controls (all $p < 0.05$).

3.2.2. Schizophrenia vs. bipolar disorder type I vs. bipolar disorder type II vs. healthy controls

For grand average MMN (Fig. 6a), we observed a significant effect of group ($F(3, 392) = 4.90$, $p = 0.002$), and a significant group × sex interaction ($F(3, 392) = 4.35$, $p = 0.005$). Pairwise post-hoc comparisons showed a significant reduction in MMN in SCZ compared to HCs ($p < 0.002$) and to BD type II ($p = 0.01$; Fig. 7). No significant differences were found between SCZ and BD type I ($p = 0.14$), between BD types I and II ($p = 0.74$), nor between HCs and BD types I and II (both $p > 0.88$). Furthermore, the post-hoc analyses showed that MMN was impaired in males with SCZ relative to male HCs ($p < 0.001$; Fig. 8) and to males with BD type II ($p = 0.03$); there were no significant MMN differences between female patients and female controls (all $p > 0.55$). There was a significant effect of repetitions ($F(2, 784) = 37.498$, $p < 0.001$), yet no significant group × repetitions or sex × repetitions interaction for MMN (all $p > 0.14$). There were no significant effects of group on MMN_{MT}, grand average RP, RP_{MT}, grand average DN, or DN_{MT} (all $p > 0.12$).

3.2.3. Bipolar disorder with or without psychosis vs. schizophrenia vs. healthy controls

ANCOVAs were then conducted in which the BD participants were grouped according to presence (BDP, $n = 26$) or absence (BDNP, $n = 39$) of lifetime history of psychosis; here, there was a significant effect of group ($F(3, 392) = 5.61$, $p < 0.001$) and a significant group × sex interaction ($F(3, 392) = 4.94$, $p = 0.002$) for grand average MMN. Post-hoc tests showed significantly reduced MMN in SCZ relative to BDNP ($p = 0.003$), but not between SCZ and BDP ($p = 0.52$). There was no significant difference between HCs, BDP, and BDNP (all $p > 0.31$). Post-hoc tests also showed significant reductions in males with SCZ compared to HC males ($p < 0.001$) and BDNP males ($p = 0.004$) and between BDP males and male controls ($p = 0.027$). There were no group differences between female patients and controls (all $p > 0.55$). There were no significant effects of group on MMN_{MT}, grand average RP, RP_{MT}, grand average DN, or DN_{MT} (all $p > 0.54$).

3.3. MMN and other clinical characteristics

In the SCZ group, there were significant associations between MMN and total PANSS score ($t = 2.12$, $\beta = 0.31$, $p = 0.041$) and GAF-F ($t = -2.37$, $\beta = -0.34$ $p = 0.028$), thus suggesting reduced amplitudes in patients with greater psychotic symptom severity and lower level of functioning. These associations were significant in male patients (PANSS: $t = 2.57$, $p = 0.018$; GAF-F: $t = -2.20$, $p = 0.041$) and not in females. Otherwise, there were no significant associations between MMN and lifetime number of psychotic and affective episodes, GAF-S, PANSS subscores according to the Wallwork-Fortgang five-factor model, MADRS, IDS and YMRS or dose of antipsychotics (all $p > 0.05$). In the BD group, there were no significant correlations between MMN and clinical characteristics (all $p > 0.05$).

4. Discussion

In this study of MMN in a cohort of clinically well-characterized patients with SCZ, BD type I and BD type II, there were five main findings. First, MMN was reduced in SCZ when compared to HCs and BD. Second, we found a significant positive correlation between MMN and total PANSS score and a significant negative correlation between MMN and GAF-F in SCZ. Third, the MMN reduction and its association with PANSS and GAF-F were only observed in males and not in females with SCZ. Fourth, there was reduced MMN in male individuals with BD with lifetime history of psychosis. Finally, we found reduced DN in males with SCZ compared to male controls.

4.1. MMN and glutamate dysregulation in schizophrenia

In the current study, we found reduced MMN in SCZ patients with a relatively moderate symptom burden. This is in line with a large body of previous research implicating MMN as a robust biomarker of SCZ (Baldeweg and Hirsch, 2015; Del Re et al., 2020; Fisher et al., 2008; Haigh et al., 2017) and the effect size ($d = 0.63$) is comparable to previous reports (Erickson et al., 2016; Light et al., 2015; Umbricht and Krljes, 2005). We also replicated previous work by showing that MMN correlated negatively with level of functioning, as indicated by GAF-F (Kaur et al., 2013; Lee et al., 2014; Light and Braff, 2005a).

The precise neural underpinnings of MMN impairment in SCZ

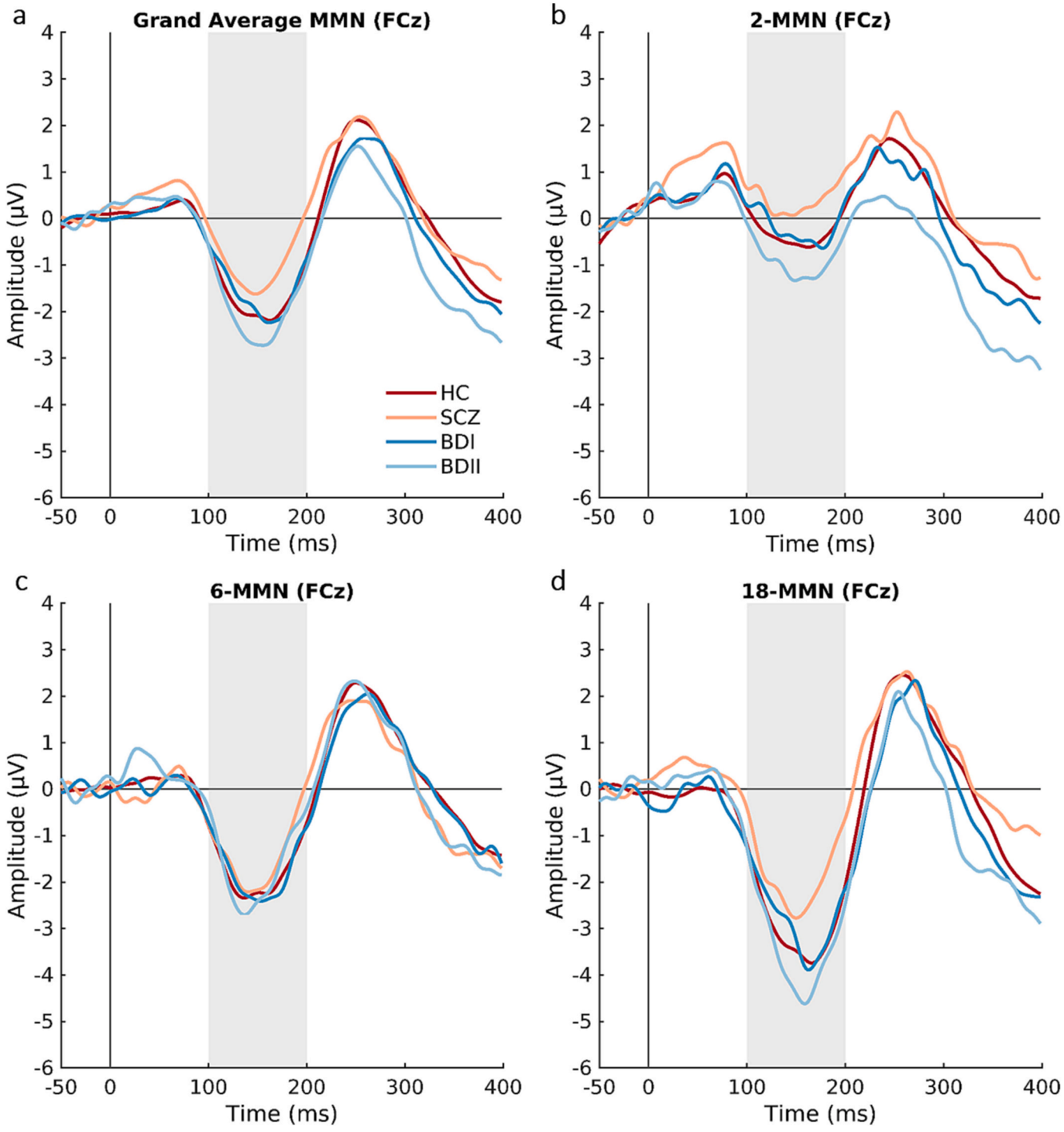

Fig. 6. Mismatch negativity (MMN) in healthy controls (HC) and individuals with schizophrenia (SCZ) or bipolar disorder type I (BDI) or II (BDII). a) illustrates the grand average MMN across 2, 6 and 18 repetitions of standard auditory stimuli, whereas b), c), and d) show MMN after 2, 6 and 18 repetitions, respectively.

remains to be fully clarified, yet is has been hypothesized that impaired function of the NMDA receptor may reduce the activity of GABAergic inhibitory interneurons and hence lead to increased glutamatergic neurotransmission through non-NDMDA receptor signaling pathways (Homayoun and Moghaddam, 2007; Lin et al., 2012). The hypothesis of glutamatergic dysregulation is supported by magnetic resonance spectroscopy studies that have demonstrated increased glutamate and glutamate/glutamine concentrations particularly in thalamic and frontal lobe regions in patients with SCZ (Dienel et al., 2020; Shah et al., 2020), which were also linked to treatment resistance (Mouchlianitis et al., 2016; Shah et al., 2020). Glutamatergic dysfunction may, in turn, cause neuronal loss due to excitotoxicity and inflammation (Baldeweg and Hirsch, 2015; Kumar et al., 2020a; Shah et al., 2020); this could, at least partly, explain the link between MMN impairment and reduced cortical volumes in frontotemporal regions (Curtis et al., 2021; Hayakawa et al., 2013; Huang et al., 2018; Kim et al., 2019; Rasser et al., 2011; Salisbury et al., 2020).

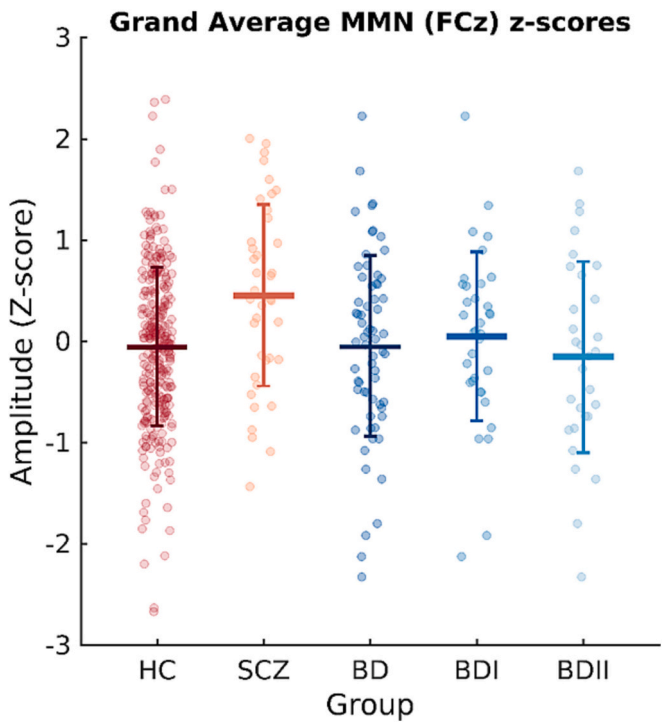

Fig. 7. Scatter plots indicating grand average mismatch negativity (MMN) across 2, 6 and 18 repetitions of standard auditory stimuli in individuals with schizophrenia (SCZ), bipolar disorder type I (BDI) and type 2 (BDII) and in healthy controls (HC). The horizontal line indicates the mean and the whiskers reflect the 1.5 interquartile range.

4.2. MMN impairment and sex

We found that MMN was reduced in males, but not in females, with SCZ. Furthermore, the associations between MMN deficit and psychosis severity and functional impairment were only observed in males. However, disease severity, patterns of substance use and indices of functioning did not differ between the sexes and are therefore unlikely to account for the male-specific results of the present work.

The MMN literature describing sex differences in neuropsychiatric disorders is scarce (Riel et al., 2019) and to our knowledge only one previous study has reported on sex differences in SCZ (Light et al., 2015), in which a small but significant reduction was noted in MMN in male vs. female patients in a large multicenter study using a classical oddball paradigm. However, when compared to HCs of the same sex, female patients with SCZ had a greater impairment than male patients (Light et al., 2015); this contrasts with the results of the present study. The roving paradigm employed by the present study may have an advantage over oddball paradigms in that differing physical characteristics of the presented stimuli are corrected for by the continuously changing tone characteristics in which a given tone acts as both standard and deviant [17]. A new auditory memory trace will thus have to be generated after each change in standard-deviant sequence. Although highly speculative, this may involve a larger population of neurons which may be differently affected in males and females with SCZ.

A greater MMN impairment in males than females with SCZ is also consistent with the notion that estrogens may exert a protective role in SCZ trough a modulatory effect on glutamatergic neurotransmission (McGregor et al., 2017; Rao and Kolsch, 2003; Seeman and Gonzalez-Rodriguez, 2021; Wickens et al., 2018) and by putative anti-inflammatory and anti-excitotoxic mechanisms (McGregor et al., 2017; Rao and Kolsch, 2003). Moreover, a recent GWAS of mood and psychotic disorders identified significant sex-dependent effects on several genes involved in neuronal excitability regulation and immune system factors, including the kynurenine pathway (Blokland et al., 2022). Kynurenine is

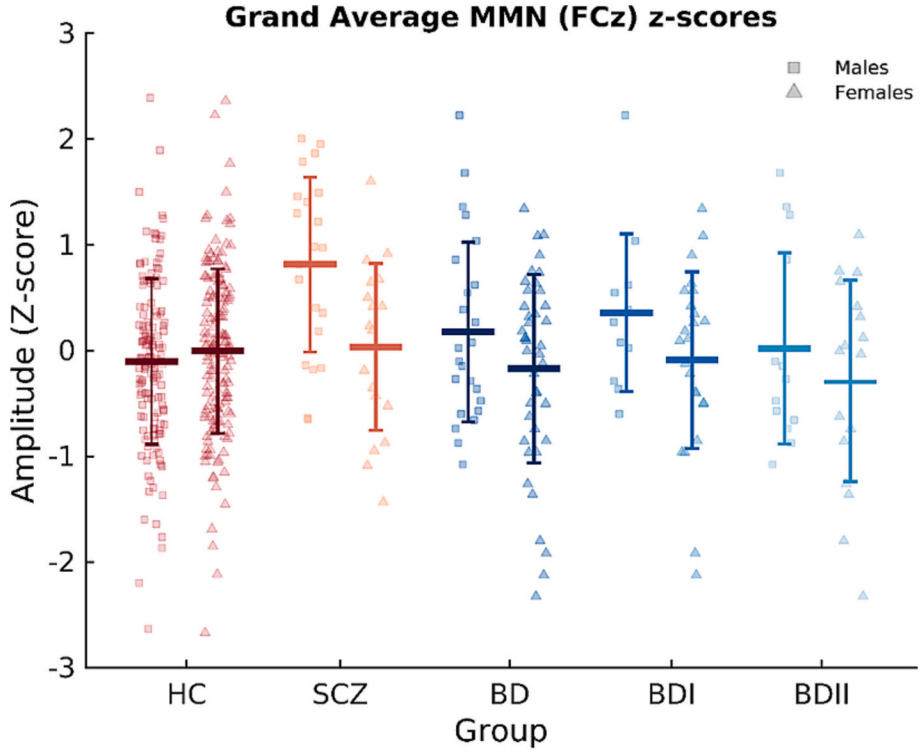

Fig. 8. Scatter plots indicating grand average mismatch negativity (MMN) across 2, 6 and 18 repetitions of standard auditory stimuli in males and females with schizophrenia (SCZ), bipolar disorder type I (BDI) and type 2 (BDII), and in healthy controls (HC). The horizontal line indicates the mean and the whiskers reflect the 1.5 interquartile range.

an endogenous NMDAR antagonist with increased levels in the cerebrospinal fluid from individuals with SCZ (Nilsson et al., 2005; Plitman et al., 2017). Thus, it can be hypothesized that sex may modulate alterations in glutamatergic neurotransmission and MMN through genetic, endocrine, and immunological factors. These effects are also potential contributors to greater functional impairment (Cotton et al., 2009; Hafner, 2003; Vila-Rodriguez et al., 2011) and overall poorer prognosis (Carpiniello et al., 2012; Novick et al., 2016) in males than females with SCZ.

4.3. MMN in bipolar disorder

In our relatively large cohort of individuals with BD, we found no reduction in MMN in the whole BD sample relative to HCs. This is in line with several previous studies (Catts et al., 1995; Hall et al., 2007; Salisbury et al., 2007; Umbricht et al., 2003), but contrary to meta-analyses showing modestly reduced MMN in BD (Featherstone et al., 2018; Hermens et al., 2018; Jahshan et al., 2012). Few studies have investigated MMN in subgroups of BD, yet one study found reduced MMN in BD versus HC, but no difference between BD types I and BD type II (Jahshan et al., 2012). However, the number of participants with BD type I and II in the present and previous studies was moderate and these may have had modest statistical power. Moreover, we employed a roving double deviant MMN paradigm, whereas a large majority of previous work used a traditional single deviant oddball paradigm. Notably, there is evidence that different test paradigms may have varying sensitivities for the detection of group differences (Kujala et al., 2007) and that more complex test paradigms may yield lower effect sizes than simpler ones (Avissar and Javitt, 2018). The fact that we did not find MMN impairment in BD could also be related to the relatively low symptom burden and high social and occupational functioning of the participants in our study.

A recent systematic review suggested MMN reduction in BD with concurrent psychosis (Raggi et al., 2021). Few studies have, however, directly compared MMN between individuals with BD with and without a life time history of psychosis (Baldeweg and Hirsch, 2015; Raggi et al., 2021). Here, we found no significant association between psychosis history and MMN impairment in the whole BD sample. However, we did find significantly reduced MMN amplitude in male participants with psychotic bipolar disorder relative to male controls. In neither males nor in the overall sample were there significant MMN differences between SCZ and bipolar disorder with a lifetime history of psychosis. Conversely, participants with non-psychotic bipolar disorder did not differ from the healthy controls in MMN amplitude. Thus, and although there was no MMN group difference between BD with and without psychosis, the results of the present study are consistent with a diagnosis-independent association between psychosis and MMN impairment (Donaldson et al., 2020; Kaur et al., 2012a; Kaur et al., 2012b; Raggi et al., 2021).

4.4. Deviance negativity, repetition positivity, and memory trace indices

There are only a few studies of the DN, RP, and their memory traces in psychotic disorders and these have yielded inconsistent results (Baldeweg and Hirsch, 2015; Baldeweg et al., 2004; McCleery et al., 2019). However, one large recent study found impaired RP_{MT} in individuals with increased psychosis risk when compared to controls and that the RP_{MT} was significantly reduced in psychosis converters when compared to non-converters (Fryer et al., 2020). In the present study, we found reduced grand average DN in males with SCZ relative to control males and a trend towards reduced memory trace of the DN in males with SCZ. Otherwise, there were no group differences in the memory trace indices of MMN, DN and RP. Further studies of the MMN, DN, and RP memory traces are thus warranted to clarify their roles as potential biomarkers in the psychoses.

4.5. Strengths and limitations

The current findings come with several strengths and limitations. Concerning the strengths, the present study included thorough clinical assessment of SCZ and BD patients, which enabled investigation of the relationships between MMN and several clinical variables. Another strength is the use of a roving paradigm that is effective in controlling for physical standard-deviant differences, which is not controlled for in conventional oddball paradigms. Regarding the limitations, it must be noted that MMN is an indirect index of glutamatergic neurotransmission and no direct measures of glutamate levels were made. The size of the patient samples was modest, and we may thus lack the statistical power to detect subgroup differences with low effect sizes. Furthermore, our work included a relatively high-functioning patient sample with moderate impairment which may have further reduced the power to detect associations between MMN and clinical characteristics. Likewise, due to the exclusion criteria, the HCs were healthier and better functioning than what would be expected in a community sample. Moreover, the present study was cross-sectional and the relationships between MMN and clinical variables, such as symptoms and medications, are best studied with a longitudinal design. Finally, and importantly, none of the exploratory analyses of the relationships between MMN and clinical variables would have remained significant after adjustments for multiple tests. The sex-specific associations between MMN and total PANSS and GAF-F scores must be confirmed by future studies.

5. Conclusions

We employed a roving paradigm and found lower MMN in moderately ill patients with SCZ than in individuals with BD and HCs, thus providing further support for MMN as a robust biomarker of SCZ. The MMN attenuation was only detected in males with SCZ and exploratory analyses indicated more severely impaired MMN in male patients with greater psychotic symptoms burden and lower level of functioning. Further studies of the relationships between MMN attenuation, symptoms clusters, and sex in SCZ are warranted.

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Declaration of competing interest

Torbjørn Elvsåshagen is a consultant to BrainWaveBank and Synovion and received speaker's honoraria from Lundbeck and Janssen Cilag.

Ole Andreassen is a consultant to HealthLytix and received speaker's honoraria from Lundbeck. The other authors declare no competing interests.

Acknowledgments

T.E. is a consultant to BrainWaveBank and Synovion and received speaker's honoraria from Lundbeck and Janssen Cilag. O.A.A. is a consultant to HealthLytix and received speaker's honoraria from Lundbeck. The other authors declare no competing interests.

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