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Evidence for Reduced Long-Term Potentiation-Like Visual Cortical Plasticity in Schizophrenia and Bipolar Disorder

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Several lines of research suggest that impairments in long-term potentiation (LTP)-like synaptic plasticity might be a key pathophysiological mechanism in schizophrenia (SZ) and bipolar disorder type I (BDI) and II (BDII). Using modulations of visually evoked potentials (VEP) of the electroencephalogram, impaired LTP-like visual cortical plasticity has been implicated in patients with BDII, while there has been conflicting evidence in SZ, a lack of research in BDI, and mixed results regarding associations with symptom severity, mood states, and medication. We measured the VEP of patients with SZ spectrum disorders (n = 31), BDI (n = 34), BDII (n = 33), and other BD spectrum disorders (n = 2), and age-matched healthy control (HC) participants (n = 200) before and after prolonged visual stimulation. Compared to HCs, modulation of VEP component N1b, but not C1 or P1, was impaired both in patients within the SZ spectrum ($\chi^2 = 35.1$, $P = 3.1 \times 10^{-9}$) and BD spectrum ($\chi^2 = 7.0$, $P = 8.2 \times 10^{-3}$), including BDI ($\chi^2 = 6.4$, $P = .012$), but not BDII ($\chi^2 = 2.2$, $P = .14$). N1b modulation was also more severely impaired in SZ spectrum than BD spectrum patients ($\chi^2 = 14.2$, $P = 1.7 \times 10^{-4}$). N1b modulation was not significantly associated with Positive and Negative Syndrome Scale (PANSS) negative or positive symptoms scores, number of psychotic episodes, Montgomery and Åsberg Depression Rating Scale (MADRS) scores, or Young Mania Rating Scale (YMRS) scores after multiple comparison correction, although a nominal association was observed between N1b modulation and PANSS negative symptoms scores among SZ spectrum patients. These results suggest that LTP-like plasticity is impaired in SZ and BD. Adding to previous genetic, pharmacological, and electrophysiological evidence, these results implicate aberrant synaptic plasticity as a mechanism underlying SZ and BD.

Key words: synaptic plasticity/EEG/visual evoked potentials/psychosis/mood states/psychotropic medication

Introduction

Schizophrenia (SZ) and bipolar disorders (BD) are severe psychiatric disorders, with a lifetime prevalence of ~0.7%[1] and ~2%,[2,3] respectively. While their precise neural substrates remain unknown, recent genetic, pharmacological, and imaging evidence implicate aberrant synaptic plasticity as a leading candidate mechanism in SZ and BD.[4–8]

Through genome-wide association studies, increased risk of SZ and BD have been associated with single nucleotide polymorphisms (SNPs) at genes linked to glutamatergic synaptic plasticity, such as *GRIN2A* and

CACNA1C.[6–11] Moreover, negative symptoms and hallucinations, both characteristic of SZ, are reliably produced by N-methyl-D-aspartate receptor (NMDAR) antagonists such as phencyclidine and ketamine,[4,12–15] further suggesting that aberrations in NMDAR-dependent synaptic function, and likely in synaptic plasticity in particular,[16] constitute a key pathophysiological mechanism in psychotic disorders.

Long-term potentiation (LTP) is a widespread class of mechanisms for induction and expression of synaptic plasticity, many of which are NMDAR-dependent.[17] A well-characterized noninvasive marker for NMDAR-dependent LTP-like visual cortical plasticity is obtainable in humans and other species by using EEG to measure modulations of visually evoked potentials (VEP) after high-frequency or prolonged visual stimulation.[18–20] In rodents, NMDAR antagonists and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) insertion-inhibitor GluR1-CT prevent VEP modulation.[21] Further, ζ inhibitory peptide, an inhibitor of Protein Kinase M-ζ, which is crucial for maintenance of LTP, disrupts the retention of VEP modulation.[22] Moreover, electric tetanus-induced LTP in the primary visual cortex modulates VEP, and inhibits further visual stimulation-induced VEP modulation.[23] Such results strongly suggest that visual stimulation-induced VEP modulation and LTP share common underlying mechanisms.

With the VEP modulation paradigm, aberrant LTP-like plasticity has been implicated in BDII,[24,25] and in major depression (MDD).[19] However, there is no previous study of VEP modulation in BDI, and results in SZ have been inconsistent,[26,27] possibly due to differences in the visual stimulation applied.[27] Efforts have been made to associate VEP modulation with symptom severity, mood states, and medication in order to assess the trait stability of VEP modulation impairments, with mixed results.[19,24,25] Thus, further evidence is required to establish impaired LTP-like synaptic plasticity as a disease characteristic in psychotic disorders.

Here, we compared patients with SZ, BDI, or BDII, and healthy controls (HCs) with respect to VEP modulation after prolonged visual stimulation, with the primary aim to examine whether LTP-like visual cortical plasticity is affected in these disorders. Further, our secondary aims were to examine (1) the pairwise differences in VEP modulation between diagnoses, (2) the association between VEP modulation and illness severity in patients, and (3) the association between VEP modulation and current use of psychotropic medications.

Methods and Materials

Participants

One hundred patients with BD type I (n = 34), BD type II (n = 33), SZ (n = 25), schizophreniform disorder (n = 3), schizoaffective disorder (n = 3), BD not otherwise specified (NOS) (n = 1), and cyclothymia (n = 1), and 411 healthy volunteers were included in this study (table 1; supplementary table S1). Since patients' ages ranged from 18 to 69 years, while ages of HCs ranged from 20 to 90 years, with means of 36.1 and 49.0 years, respectively, all analyses were performed using an age-matched HC sample

Table 1. Sample Characteristics

	HC (n = 200)	SZ (n = 31)	BD (n = 69)	P
Age	38.2 (11.1)	36.7 (11.6)	35.9 (12.5)	.31
Sex (f/m)	112/88	14/17	46/23	.11
IQ	114.9 (10.6)	104.8 (13.7)	114.5 (11.8)	3.3×10^{-5}
Illness duration (years)	–	10.5 (9.4)	10.4 (10.2)	.98
MADRS	1.8 (2.7)	12.5 (6.2)	14.5 (9.6)	1.3×10^{-68}
YMRS	0.9 (1.5)	3.8 (4.7)	4.0 (4.9)	4.0×10^{-15}
PANSS positive	–	13.8 (4.8)	8.6 (2.2)	1.8×10^{-13}
PANSS negative	–	15.1 (5.5)	9.4 (3.0)	5.3×10^{-11}
IDS sleep items	1.6 (1.8)	4.1 (2.3)	3.8 (2.5)	5.8×10^{-19}
No psychotropics	200	5	15	1.3×10^{-47}
Antipsychotics	0	22	25	3.6×10^{-29}
Antiepileptics (T/L/V/Pr/U)	0	2/1/1/0/0	25/19/3/1/2	1.2×10^{-18}
Antidepressants	0	5	28	1.1×10^{-19}
Anxiolytics/hypnotics	0	2	6	2.2×10^{-4}
Lithium	0	1	9	1.3×10^{-6}
Tobacco daily (y/n)	43/148	13/17	28/39	.002
Cannabis last month (y/n)	5/187	3/25	7/57	.016
Alcohol last day (y/n)	41/152	1/27	10/54	.06
Coffee daily (y/n)	137/56	23/8	47/20	.92

Note: Values represent either number of participants, or mean and standard deviation. HC, Healthy controls; SZ, schizophrenia spectrum; BD, bipolar disorders; P, Probability of no difference between the 3 groups; MADRS, Montgomery and Asberg Depression Rating Scale; YMRS, Young Mania Rating Scale; PANSS, Positive and Negative Symptoms Scale; IDS, Inventory of Depressive Symptoms; T/L/V/Pr/U, Total antiepileptics/Lamotrigine/Valproate/Pregabaline/Unspecified.

(n = 200, age range: 20–70, mean age: 38.2), drawn using the nearest neighbor method in the 'MatchIt' package in R.[28] Patients were recruited through psychiatric in- and outpatient treatment units in the Oslo area, while HCs were recruited through national records and advertisements in a regional newspaper.[29] Participants with neurological disorders or moderate to severe head injury at any time in their life, were excluded from the study. All participants had normal or corrected-to-normal vision. The study was approved by the Regional Ethical Committee of South-Eastern Norway, and all participants provided written informed consent.

Clinical and Neuropsychological Assessment

Patients were diagnosed by trained clinicians using the Structured Clinical Interview for the DSM-IV, Axis I disorders (SCID-I).[30] Participants were evaluated for IQ, using the Wechsler Abbreviated Scale of Intelligence (WASI).[31] Number of previous psychotic episodes, defined as an episode with score of ≥4 on Positive and Negative Syndrome Scale (PANSS)[32] items p1-3, p5, p6, or g9 for ≥1 week, was assessed. Current symptoms severity were evaluated using the PANSS positive and negative symptoms scores, the Montgomery and Åsberg Depression Rating Scale (MADRS),[33] and the Young Mania Rating Scale (YMRS).[34] Current sleep disturbances were evaluated with the 4 sleep-related items of the Inventory of Depressive Symptoms (IDS).[35] Daily doses of antipsychotics and antiepileptics were normalized against defined daily doses for each specific drug to yield standardized doses within drug class for each patient.

Visual Evoked Potentials

The VEP modulation paradigm was adopted from Normann et al,[19] and all experimental procedures were performed as described previously,[36] with postintervention VEPs assessed at 120 s and 220 s (post 1), 380 s and 480 s (post 2), ~30 min and ~32 min (post 3), and ~54 min and ~56 min (post 4) after 10 min of checkerboard stimulation at a spatial frequency of 1 cycle/degree and a temporal frequency at 2 reversals per second (figure 1). To monitor constant fixation throughout the experiment, all participants focused on a fixation point at the centre of the screen and were asked to press a button when it changed color. EEG was recorded from a BioSemi ActiveTwo amplifier, with 64 Ag-AgCl sintered electrodes distributed across the scalp according to the international 10–20 system, and 4 electrodes located around the eyes to acquire horizontal and vertical electro-oculograms. Potentials at each channel were sampled at 2048 Hz with respect to a common mode sense, with a driven right leg electrode minimizing common mode voltages. Participants completed a mismatch negativity paradigm and a pre-pulse inhibition paradigm between postintervention assessments 2 and 3, and 3 and 4, respectively (figure 1).

Signal processing was performed using MATLAB and the EEGLAB toolbox.[37] Offline, recordings were downsampled to 512 Hz. Noisy channels were removed using PREP pipeline[38] with default settings, before re-referencing to remaining channel average, interpolation of removed channels, and finally a second re-referencing to the post-interpolation average. Data were band pass-filtered between 0.1 and 40 Hz. Event markers were adjusted to account for a latency of 20 ms in the visual presentation, measured with a BioSemi PIN diode, before epoch extraction at 200 ms pre- to 500 ms post-stimulus, and subsequent baseline correction. Artifactual muscle, eye blink, and eye movement components were removed with SASICA[39] using default parameters after independent component analysis using the SOBI algorithm. Epochs with a drift exceeding 100 μV were removed, and channels were re-referenced to the AFz electrode.

VEPs were averaged according to subject and pairs of blocks (baseline, post 1, post 2, post 3, and post 4), and components C1, P1, and N1b were extracted from the Oz electrode as the minimum amplitude between 50 and 100 ms post-stimulus, maximum amplitude between 80 and 140 ms, and mean amplitude between the first negative and halfway to the first positive peak after P1 (~150–190 ms post-stimulus), respectively. Components C1, P1, and N1b were selected on the basis of previous results strongly suggesting that, using the reversing checkerboard VEP modulation paradigm, modulation of components C1, P1, and particularly N1b constitute robust measures of LTP-like synaptic plasticity.[36] Since previous studies have also reported data on N1 peak modulation,[19] and P1-N1 peak-to-peak modulation,[24,25] we report corresponding data in the supplementary material. Data was selected from the Oz electrode on the basis of previous results strongly favoring this channel for VEP modulation

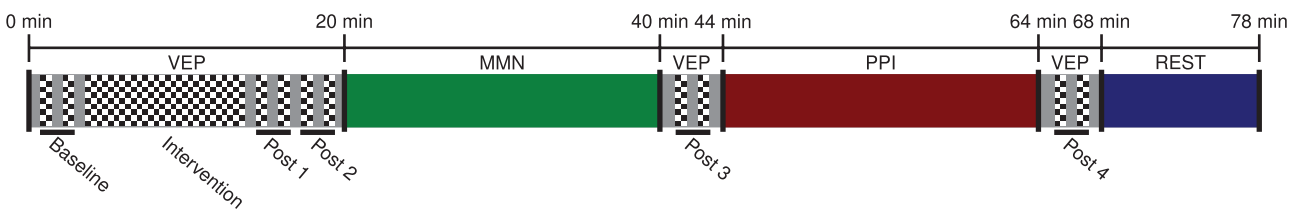

Fig. 1. Experimental timeline. VEP, visually evoked potential paradigm; MMN, mismatch negativity paradigm; PPI, prepulse inhibition paradigm; REST, resting state EEG.

assessments using the reversing checkerboard with prolonged visual stimulation paradigm.[36] Further, supplementary figure S1 shows that the Oz channel is a robust source for data extraction with the reversing checkerboard VEP modulation paradigm in all groups of the current study.

Statistical Analysis

Statistical analysis was performed in R version 3.6.1.[40] For all analyses except sensitivity analyses for separate diagnoses, patients with SZ, schizophreniform disorder, and schizoaffective disorder were considered conjointly, as were patients with BDI, BDII, BD NOS, and cyclothymia, with the resulting groups being referred to as SZ spectrum disorders ($n = 31$) and BD spectrum disorders ($n = 69$), respectively.

Participants with outlying difference scores (baseline amplitudes subtracted from post-intervention amplitudes) for a VEP component (C1, P1, or N1b) at 1 or more post-intervention assessments had all their postintervention assessments excluded from analysis for that particular component. Outliers were identified according to the median absolute deviation procedure implemented in R package 'Routliers',[41] with 3 median absolute deviations as threshold, yielding 13 outliers for N1b modulation (SZ spectrum: 1, BD spectrum: 2, and HC: 10). This procedure ensured a normal distribution of linear model residuals.

All analyses, except tests of baseline VEP component amplitudes, were performed directly on difference scores. Linear models were evaluated with type-II analyses of deviance implemented in R package 'car'[42] to yield unbiased estimates of χ^2 along with *P*-values for each predictor, or *t*-scores for intercepts. Outcomes that were not changing over time were assessed with 2-tailed *t*-tests. All *P*-values are reported in uncorrected form, whereas significance thresholds were adjusted according to the effective number of independent comparisons within sets of analyses, by Sidak[43] or Bonferroni correction for continuous or categorical variables, respectively. This procedure yielded an $\alpha = 0.020$ for primary analyses, ie, modulation of C1, P1, and N1b modeled by diagnosis, time, and diagnosis × time, and for secondary analyses: (1) $\alpha = 0.016$ in the pairwise comparisons of N1b modulation between diagnoses, (2) $\alpha = 0.012$ in the models of clinical variables with N1b modulation as predictor, and (3) $\alpha = 0.010$ in the models of N1b modulation with groups of psychotropic medications as predictors. The series of sensitivity tests, that were performed to examine the robustness of primary or secondary results, inherited significance thresholds from their parent analysis. Lastly, in the 2-step analyses of associations between clinical variables and N1b modulation, we used an uncorrected significance threshold in the first step testing for interaction effects between N1b modulation and diagnosis, in order to minimize the probability of, in the second step, pooling together groups with different association slopes.

Results

N1b Modulation is Reduced in SZ and BD Spectrum Disorders

In this sample, there was modulation of VEP components C1 ($t = 14.1$, $P = 9.9 \times 10^{-42}$), P1 ($t = 11.9$, $P = 4.7 \times 10^{-31}$), and N1b ($t = -18.3$, $P = 9.5 \times 10^{-66}$) after prolonged visual stimulation (figures 2B–H). Further, there was no significant association between diagnosis and baseline amplitudes of either component C1 ($\chi^2 = 3.4$, $P = .18$), P1 ($\chi^2 = 1.1$, $P = .54$), or N1b ($\chi^2 = 4.6$, $P = .10$; figure 2A).

The general linear model for N1b modulation with diagnostic group (SZ spectrum vs BD spectrum vs HC), time (post-intervention assessments 1 vs 2 vs 3 vs 4), and diagnostic group × time interaction as predictors revealed an effect of diagnostic group ($\chi^2 = 37.9$, $P = 5.9 \times 10^{-9}$) and time ($\chi^2 = 51.1$, $P = 4.6 \times 10^{-11}$) on modulation of VEP component N1b (figure 2H; table 2; supplementary figure S2), with no interaction effect ($\chi^2 = 1.4$, $P = .97$), demonstrating that N1b modulation was different between the diagnostic groups, and that N1b modulation waned over time across diagnostic groups. Corresponding general linear models did not demonstrate differences between diagnostic groups in the modulation of components C1 ($\chi^2 = 0.5$, $P = .78$, figure 2F) or P1 ($\chi^2 = 2.7$, $P = .25$, figure 2G), and further analyses for these components were not pursued.

Pairwise comparisons showed that modulation of N1b after prolonged visual stimulation was impaired in patients with SZ spectrum ($\chi^2 = 35.0$, $P = 3.1 \times 10^{-9}$) and in patients with BD spectrum disorders ($\chi^2 = 7.0$, $P = 8.2 \times 10^{-3}$) relative to controls. The impairment was more pronounced in SZ spectrum than in BD spectrum disorders ($\chi^2 = 14.1$, $P = 1.8 \times 10^{-4}$, figure 2H). Moreover, sensitivity analyses of separate diagnoses showed that N1b modulation was reduced in SZ alone ($\chi^2 = 35.9$, $P = 2.1 \times 10^{-9}$) and in BDI alone ($\chi^2 = 6.4$, $P = .012$), but not in BDII alone ($\chi^2 = 2.2$, $P = .14$).

We performed a series of sensitivity tests to examine the robustness of the effect of diagnosis on N1b modulation. The effect of diagnosis on N1b modulation remained significant when controlling for baseline amplitudes, sex, and age ($\chi^2 = 28.5$, $P = 6.6 \times 10^{-7}$), when controlling for mood states, as indexed by MADRS and YMRS ($\chi^2 = 9.3$, $P = 6.5 \times 10^{-5}$), and when controlling for IQ ($\chi^2 = 21.2$, $P = 2.5 \times 10^{-5}$), current sleep disturbance ($\chi^2 = 30.2$, $P = 2.8 \times 10^{-7}$), and daily use of tobacco, monthly use of cannabis, or use of alcohol within the last day before examination ($\chi^2 = 32.0$, $P = 1.1 \times 10^{-7}$). Further, the effect of diagnosis on N1b modulation

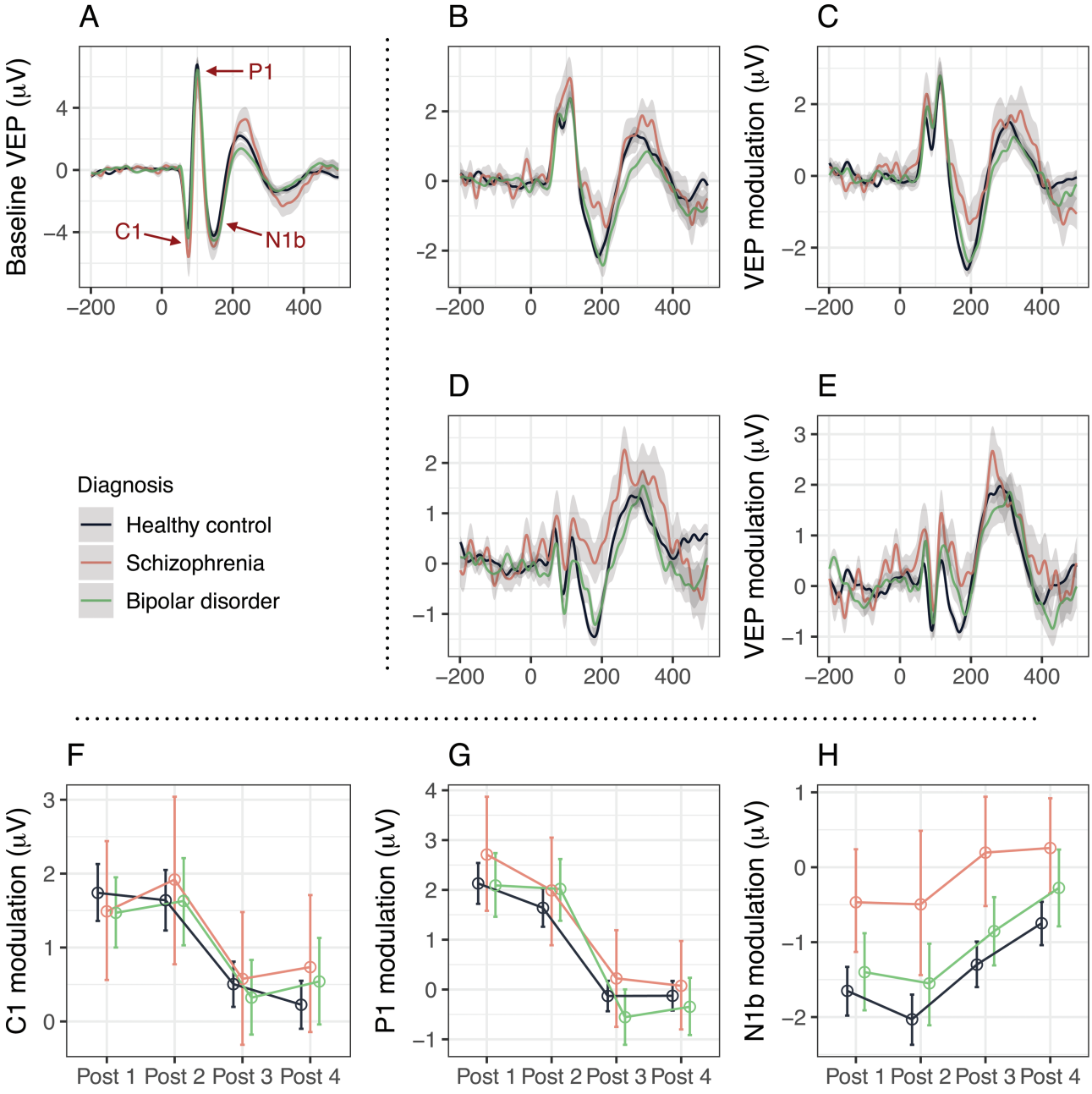

Fig. 2. (A) Visually evoked potentials (VEP) at baseline, by diagnostic group. VEPs were measured at the occiput (Oz), with anterior reference (AFz). (B) VEP modulation (baseline VEP subtracted from postintervention VEP) at postintervention assessment 1 (2–4 min after prolonged visual stimulation), by diagnostic group. (C) VEP modulation at postintervention assessment 2 (6–8 min after prolonged visual stimulation), by diagnostic group. (D) VEP modulation at postintervention assessment 3 (30–32 min after prolonged visual stimulation), by diagnostic group. (E) VEP modulation at postintervention assessment 4 (54–56 min after prolonged visual stimulation), by diagnostic group. (F) C1 modulation (baseline C1 amplitudes subtracted from postintervention C1 amplitudes) at postintervention assessments 1–4, by diagnostic group. No difference in C1 modulation was detected between diagnostic groups ($\chi^2 = 0.5$, $P = .78$). (G) P1 modulation at postintervention assessments 1–4, by diagnostic group. No difference in P1 modulation was detected betweeen diagnostic groups ($\chi^2 = 2.7$, $P = .25$). (H) N1b modulation at postintervention assessments 1–4, by diagnostic group. N1b modulation was significantly different between healthy controls, bipolar disorder (BD) patients, and schizophrenia (SZ) spectrum patients ($\chi^2 = 37.9$, $P = 5.9 \times 10^{-9}$).

remained significant when considering only unmedicated patients ($n = 20$) against HCs ($\chi^2 = 18.7$, $P = 8.7 \times 10^{-5}$). The effect of diagnosis on N1b modulation also was significant in the model where outliers were included ($\chi^2 = 29.1$, $P = 4.8 \times 10^{-7}$). Lastly, although due to an error in the gaming controller used for responses to on-screen dot color changes, these response data were missing for 40.4% of the current sample, there were no significant

group differences in missing rates ($\chi^2 = 6.0$, $P = .20$), nor in the proportion of correct responses to the on-screen dot color changes ($t = -0.4$, $P = .71$), indicating that the attention afforded to the prolonged visual stimulation did not differ between patients and controls.

Associations Between N1b Modulation and Clinical States

First, using the patient sample, we tested the interaction effect between N1b modulation and diagnosis in models for clinical variables with N1b modulation, diagnosis, and time (postintervention assessments 1–4), and interactions between them, as predictors. This interaction was significant in the model for PANSS negative symptoms scores ($\chi^2 = 6.1$, $P = .013$), but not for PANSS positive symptoms scores ($\chi^2 = 0.4$, $P = .51$), number of psychotic episodes ($\chi^2 = 1.2$, $P = .28$), MADRS scores ($\chi^2 = 0.0$, $P = .97$), or YMRS scores ($\chi^2 = 0.6$, $P = .43$). Therefore, the association between PANSS negative symptoms scores and N1b modulation was tested separately in SZ spectrum and in BD patients, while the other associations between clinical variables and N1b modulation were tested with diagnosis as a covariate. The association between PANSS negative symptoms scores and N1b modulation was nonsignificant in BD patients ($\chi^2 = 1.1$, $P = .30$), and in SZ spectrum patients ($\chi^2 = 6.0$, $P = .015$), according to the corrected α threshold. The trending association between PANSS negative symptoms scores and N1b modulation in SZ spectrum patients was positive, which, since N1b modulation is in the negative direction, indicates more aberrant N1b modulation with higher PANSS negative symptoms scores. Further, there was no association in patients between N1b modulation and PANSS positive symptoms scores ($\chi^2 = 0.6$, $P = .44$), number of psychotic episodes ($\chi^2 = 0.5$, $P = .49$), MADRS scores ($\chi^2 = 0.8$, $P = .36$), or YMRS scores ($\chi^2 = 0.0$, $P = .94$; figures 3A–E).

Table 2. N1b Modulation by Diagnosis

	HC (*d*, 95% CI)	SZ (*d*, 95% CI)	BD (*d*, 95% CI)
Post 1	−0.71, [−0.85, −0.57]	−0.24, [−0.60, 0.12]	−0.65, [−0.88, −0.41]
Post 2	−0.86, [−1.00, −0.71]	−0.19, [−0.55, 0.18]	−0.66, [−0.90, −0.43]
Post 3	−0.60, [−0.75, −0.46]	0.10, [−0.27, 0.46]	−0.44, [−0.68, −0.20]
Post 4	−0.37, [−0.51, −0.22]	0.15, [−0.22, 0.51]	−0.13, [−0.36, 0.11]

Note: Modulation of VEP component N1b at post 1–4 assessments for participants with schizophrenia spectrum disorder (SZ), bipolar spectrum disorders (BD), or healthy controls (HC).

N1b Modulation is Further Reduced in Patients Using Antiepileptic or Antipsychotic Medication

Across all patients, N1b modulation was lower in users of antipsychotic medication ($\chi^2 = 8.3$, $P = 3.9 \times 10^{-3}$), with a similar trend observed in users of antiepileptic medication ($\chi^2 = 3.5$, $P = .062$), than in non-users. In BD patients, N1b modulation was more severely impaired among users of antiepileptics ($\chi^2 = 9.3$, $P = 2.3 \times 10^{-3}$, figure 4A), and nominally in users of antipsychotics ($\chi^2 = 4.4$, $P = 0.035$, figure 4B). Further, the association in BD patients between lamotrigine and N1b modulation ($\chi^2 = 6.8$, $P = 8.9 \times 10^{-3}$) was comparable to the effect of antiepileptics in general. Within BDII patients only, N1b modulation was still lower among users of antiepileptics ($\chi^2 = 9.1$, $P = 2.5 \times 10^{-3}$, $n = 11$), and nominally lower among users of antipsychotics ($\chi^2 = 4.7$, $P = .03$, $n = 7$). However, within BDI patients only, N1b modulation did not remain significantly lowered among users of antiepileptics ($\chi^2 = 3.2$, $P = .07$, $n = 11$), nor among users of antipsychotics ($\chi^2 = 0.6$, $P = .45$, $n = 17$). There was no evidence for lowered N1b modulation among antipsychotics users with SZ spectrum disorder ($\chi^2 = 0.1$,

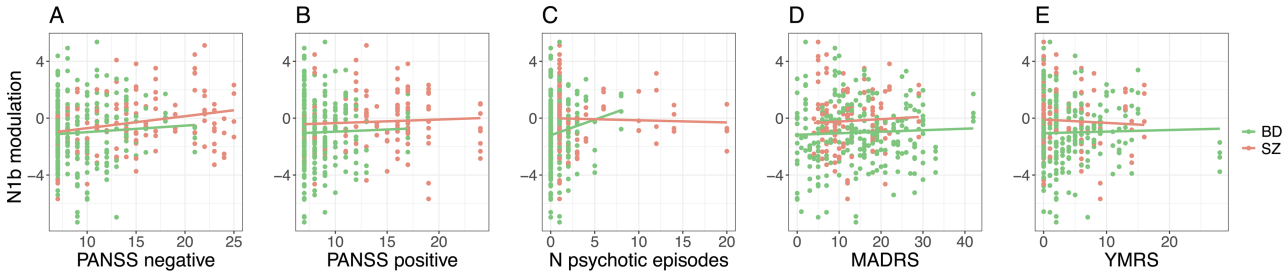

Fig. 3. Associations between clinical states and N1b modulation in patients, at postintervention assessments 1–4. (A) Associations between N1b modulation and Positive and Negative Syndrome Scale (PANSS) negative symptoms scores did not reach the corrected significance threshold in SZ spectrum patients ($\chi^2 = 6.0$, $P = .015$) or in BD patients ($\chi^2 = 1.1$, $P = .30$; diagnoses considered separately because the interaction effect of N1b modulation × diagnosis was significant at an uncorrected significance threshold). The nominally significant negative association between N1b modulation and PANSS negative symptoms scores in SZ spectrum patients indicates greater impairments in long-term potentiation (LTP)-like plasticity among SZ spectrum patients with a higher burden of negative symptoms. (B) N1b modulation was not associated with PANSS positive symptoms scores in patients ($\chi^2 = 0.6$, $P = .44$). (C) N1b modualation was not associated with number of psychotic episodes in patients ($\chi^2 = 0.5$, $P = .49$). (D) N1b modulation was not associated with Montgomery and Åsberg Depression Rating Scale (MADRS) scores in patients ($\chi^2 = 0.8$, $P = .36$). (E) N1b modulation was not associated with Young Mania Rating Scale (YMRS) scores in patients ($\chi^2 = 0.0$, $P = .94$).

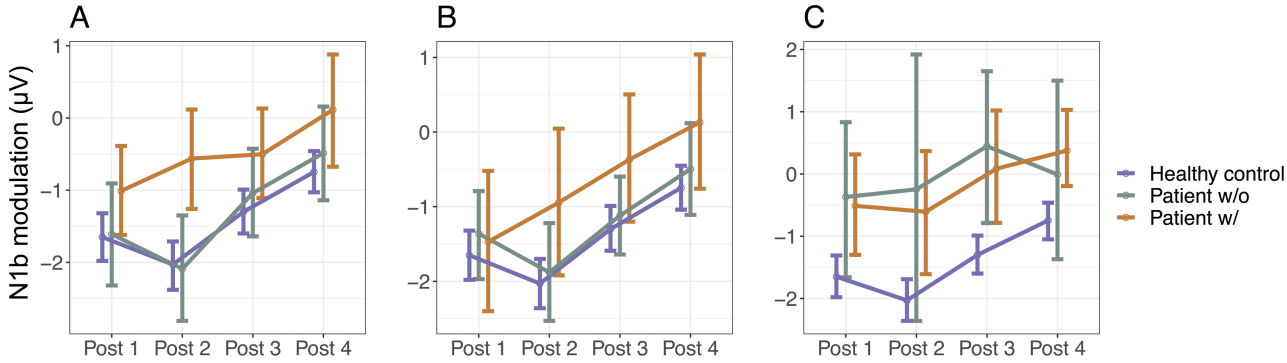

Fig. 4. (A) Antiepileptics use in patients with BD. N1b modulation at postintervention assessments 1–4 was lower in BD patients using antiepileptics (w/) than in BD patients not using antiepileptics (w/o) ($\chi^2 = 9.3$, $P = 2.3 \times 10^{-3}$). N1b modulation for healthy controls is represented for comparison. (B) Antipsychotics use in patients with BD. N1b modulation at postintervention assessments 1–4 was tendentially lower in BD patients using antipsychotics (w/) than in BD patients not using antipsychotics (w/o) ($\chi^2 = 4.4$, $P = .035$). (C) Antipsychotics use in patients with SZ spectrum disorders. N1b modulation at postintervention assessments 1–4 was not significantly different between SZ spectrum patients using antipsychotics (w/) and SZ spectrum patients not using antipsychotics (w/o) ($\chi^2 = 0.1$, $P = .70$).

$P = 0.70$, figure 4C), and only one SZ spectrum patient used antiepileptics.

Further, when controlling for diagnosis and YMRS scores, the association between antiepileptics use and N1b modulation remained significant ($\chi^2 = 9.0$, $P = 2.6 \times 10^{-3}$). Standardized antiepileptics dose was only nominally significantly associated with N1b modulation when controlling for diagnosis ($\chi^2 = 6.4$, $P = .011$), while standardized antipsychotics dose was significantly associated with N1b modulation when controlling for diagnosis ($\chi^2 = 11.5$, $P = 6.9 \times 10^{-4}$). Further, when controlling for diagnosis, and positive and negative symptoms as indexed by PANSS, the association with reduced N1b modulation remained for antiepileptics use ($\chi^2 = 14.4$, $P = 1.5 \times 10^{-4}$), but not for antipsychotics use ($\chi^2 = 1.8$, $P = .18$). Since psychotropic medication use was associated with reduced N1b modulation in BD patients, and since antiepileptic use, in particular, was still associated with reduced N1b modulation in BD patients when controlling for YMRS scores, and PANSS negative and PANSS positive symptoms scores, we tested whether BD patients not using antiepileptics ($n = 44$) still differed from HC participants in N1b modulation, which they did not ($\chi^2 = 0.4$, $P = .51$). On the other hand, N1b modulation was markedly lower in BD patients using antiepileptics ($n = 25$) than in HC participants ($\chi^2 = 15.9$, $P = 6.6 \times 10^{-5}$). Finally, there was no evidence for any change in N1b modulation among patients using either lithium ($\chi^2 = 0.6$, $P = .43$), antidepressants ($\chi^2 = 1.3$, $P = .25$), or anxiolytics/hypnotics ($\chi^2 = 1.5$, $P = .22$).

Discussion

This study of LTP-like visual cortical plasticity in patients with SZ, BDI, and BDII, and HCs, yielded 4 main results. First, relative to age-matched HCs, modulation of the N1b component of the VEP after prolonged visual stimulation was significantly reduced in SZ and BDI, but not BDII patients. Second, N1b modulation was reduced in patients using antiepileptics or antipsychotics. Third, we did not observe any significant associations between N1b modulation and mood states, nor between N1b modulation and PANSS positive or PANSS negative symptoms scores when controlling for diagnosis. Finally, we did not observe any significant difference between patients with BD or SZ spectrum disorders and HCs in the modulation of VEP components C1 or P1.

Modulation of VEP components in general, and the N1b component in particular, has been implicated as a candidate index of NMDAR-dependent LTP-like plasticity in the visual cortex. In humans, N1b modulation is dependent on high-frequency visual stimulation,[20] and N1 modulation, strongly associated with N1b modulation,[36] has been demonstrated to depend on prolonged visual stimulation.[19] N1b modulation after prolonged visual stimulation seems to have a more robust response and a time-course more compatible with LTP than the modulation of other VEP components.[36] Further, using checkerboard stimulation, N1 modulation has been observed to be specific to frequency and pattern of the intervention stimulus.[19] Similarily, modulation of sine grating-elicited N1b after high-frequency visual stimulation is orientation- and spatial frequency-specific in humans, indicating a synapse specificity of N1b modulation similar to LTP.[44,45] The result that N1b component modulation after visual stimulation is reduced in SZ and BDI patients is therefore in line with previous genetic[5,6] and pharmacological evidence,[4,12–15] strengthening the hypothesis that NMDAR-dependent synaptic plasticity is affected in these disorders.[16]

The present results provide a demonstration of reduced N1b modulation in patients with BDI, an association that has not been examined previously. Further, the present results provide a clear demonstration of reduced N1b modulation in patients with SZ. Previously,

2 separate studies have compared VEP modulation between SZ patients and HCs, with the first study showing evidence for reduced N1b modulation in SZ,[26] whereas the second study found no evidence for altered VEP modulation in SZ.[27] In the former study,[26] modulation of component C1 was also decreased in SZ patients, albeit with lower certainty than for the N1b component. Rather than a checkerboard stimulus, the latter study used a grating stimulus, which is well suited for manipulating stimulus orientation and assessing the input specificity of modulation effects, as well as an intermittent on/off stimulation pattern during intervention, and varying levels of visual contrast (predominantly at 35%) rather than visual contrast fixed at 100%. As described by the authors, 1 or more of these conditions may have contributed to lower effect sizes and accordingly lower power in detecting group differences.[27] Previously, 2 studies have compared VEP modulation between BDII patients and HCs.[24,25] While both of these observed a tendency of reduced P1 modulation in BDII patients, and both observed reduced P1-N1 peak-to-peak modulation in BDII patients, the relationship observed in these studies between BDII diagnosis and N1b modulation is less clear, since the component N1b was not extracted. However, there was a tendency in one of the studies of reduced modulation in BDII patients of N1,[25] a component that is correlated with N1b,[36] comparable to the tendency of reduced N1b modulation in BDII patients observed in the present sample. Taken together, these converging results suggest that N1b modulation after prolonged visual stimulation, likely indexing NMDAR-dependent synaptic plasticity in the visual cortex,[21–23] is reduced in SZ and BDI, and, possibly to a lesser extent, in BDII.

Reduced N1 peak modulation, highly correlated with N1b modulation, has previously been observed also in MDD patients.[19] Although the present results strongly suggest that N1b modulation is particularly affected in patients with SZ spectrum disorders, results in BD and MDD demonstrate that VEP modulation deficits are not specific to SZ spectrum disorders. This is in line with recent findings of shared genetic architecture between these disorders.[46,47] Conversely, we demonstrate in SZ and BD patients modulation of components C1 and P1 that is comparable to that of HCs, raising the question of whether VEP modulation deficits in psychiatric disorders might be specific to the N1b component. Other studies have shown reduced C1 modulation in SZ patients[26] and tendencies of reduced P1 modulation in BDII patients,[24,25] suggesting that this might not be the case. Nevertheless, associations between diagnosis and modulation of components C1 and P1 are absent in the present data, even though modulation of these VEP components are moderately correlated with N1b modulation in controls.[36] These results, along with differences in modulation duration described previously,[36] suggest that C1, P1, and N1b modulation might reflect different underlying mechanisms.

Further, we found no significant associations after multiple comparison correction between N1b modulation and either of the clinical variables, ie, PANSS negative symptoms scores, PANSS positive symptoms scores, number of psychotic episodes, MADRS scores, or YMRS scores. However, in the model for PANSS negative symptoms scores, the interaction effect of N1b modulation and diagnosis was significant (albeit at an uncorrected significance threshold), and the positive association between PANSS negative symptoms scores and N1b modulation was nominally significant in SZ spectrum patients. This indicates that higher negative symptom severity could be related to larger impairments in LTP-like plasticity, and further studies are needed to clarify the relationship between PANSS scores and N1b modulation.

Reduced N1b modulation was also associated with use of some classes of psychotropic medication among patients in a manner depending on diagnosis. First, use of antiepileptics, particularly lamotrigine, was associated with reduced N1b modulation in BD patients. Further, the association between antiepileptics use and reduced N1b modulation remained significant after controlling for specific diagnosis and for PANSS negative and positive symptoms scores, and after controlling for specific diagnosis and YMRS scores. Thus, the decreased N1b modulation among antiepileptics users is likely not explained by diagnosis or by psychotic or manic symptom severity and we cannot rule out that the reduced N1b modulation in BD patients is affected by antiepileptics. Although the extent to which antiepileptics decrease the probability of NMDAR-dependent synaptic plasticity remains to be clarified, antiepileptics promote $GABA_A$-mediated inhibition, increase sodium channel resistance, inhibit glutamate release,[48,49] and decrease LTP in hippocampal slices.[50] Lamotrigine likely inhibits glutamate release through increasing sodium channel resistance, which could potentially contribute to the reduced N1b modulation. However, future longitudinal pharmacological studies using a randomized controlled design would be needed to carefully test this hypothesis. Second, antipsychotics use was associated with reduced N1b modulation among BD patients, but not among SZ spectrum patients. Further, standardized dose of antipsychotics was associated with reduced N1b modulation even controlling for diagnosis. However, the association between N1b modulation and antipsychotics use did not remain significant after controlling for diagnosis and PANSS negative and positive symptoms scores, suggesting that these associations could reflect intrinsic differences (eg, symptom severity) in antipsychotics users vs non-users, and in recipients of different doses, rather than a direct effect of antipsychotics use on LTP-like plasticity. Third, we did not observe an association between antidepressant use and N1b modulation, in contrast to previous experimental results demonstrating increased LTP-like plasticity with SSRI treatment.[19] In this previous study,

antidepressant were given to HCs for 3 weeks with within-subject pre-treatment and post-treatment assessments of LTP-like plasticity, while in the present study, we tested associations between antidepressant use and LTP-like plasticity in patients who had been using antidepressants in combination with other psychotropic drugs over longer periods of time. Any of these differences in sample, time on drugs, and design, could potentially explain the differences between this and the previous study with regards to the relationship between antidepressant use and LTP-like plasticity.

Conclusion

The present study demonstrated impaired LTP-like plasticity in patients with SZ and BDI, but not in patients with BDII. Together with previous genetic, pharmacological, and anatomical research, these results implicate aberrant synaptic plasticity as a pathophysiological mechanism in SZ and BD.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin* online.

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