

Comparison of automatic visual attention in schizophrenia, bipolar disorder, and major depression: Evidence from P1 event-related component

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Aim: The ability to discern commonalities and differences in the neurobiology of functional psychoses represents a key element to unmasking shared vulnerability across different psychiatric conditions. The present study sought to compare the automatic visual attention mechanisms in three psychiatric disorders considered to distribute along the continuum of psychosis severity: schizophrenia (SCZ), bipolar disorder (BD), and major depressive disorder (MDD). To this end, the visual P1 event-related potential component, a cortical correlate of automatic visual attention, was measured during an ecological task based on visual word pair presentation.

Methods: Four samples of participants, 18 SCZ, 20 BD, 28 MDD, and 30 healthy controls, were recruited and submitted to the same procedure and stimuli. The P1 evoked by visual word presentation was recorded through a 38-electrode electroencephalography cap. Words were presented on a computer screen serially as pairs, and participants had to decide whether they rhymed or not.

Results: P1 was larger at posterior sites in SCZ compared with BD, healthy control, and MDD participants. BD patients showed the lowest P1 compared with all other groups. Positive Pearson's correlations were found in SCZ patients between P1 amplitude on left posterior sites and both hallucination severity and worse task performance.

Conclusion: The three investigated psychiatric samples showed different automatic visual attention patterns: SCZ patients exhibited the greatest cognitive impairment correlated with the amplitude of P1, MDD patients revealed a normal component, and BD showed a compensated euthymic response different from results of past literature in untreated patients.

Keywords: bipolar disorder, event-related potentials, major depressive disorder, psychotic spectrum disorders, schizophrenia.

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Schizophrenia (SCZ) is a major chronic psychiatric disorder characterized by a complex and multifaceted symptomatology, which leads to severe disability.¹ Over the last years, several pieces of evidence have shown that SCZ shares many similarities and overlap with other psychiatric illnesses (i.e., delusions and positive symptomatology in SCZ and mania in bipolar disorder [BD]),² but this diagnostic issue makes successful identification and treatment of this condition still very complex. Moreover, these similarities suggest that the clinical and diagnostic boundaries between these conditions are not as strong as was thought in the past, and that they should be rather considered as disorders belonging to a continuum spectrum. Recent advances in the neurobiological and genetic characterization of these diseases support the idea of a continuum across psychotic manifestations,³ which has also been included in the DSM-5⁴ and has been proposed as the main core of the Research Domain Criteria (RDoC) approach toward psychoses.⁵ Nevertheless, this characterization sought to identify measures that could help in the description of similarities and differences across patients, with the main goal of improving the diagnostic tools available for clinical practice.

Abnormal functioning of early attentional mechanisms has long been claimed as a core feature of SCZ.⁶ This impairment consists in a

reduced ability to filter out sensory information that is irrelevant for the ongoing task, leading to an information overload that affects all the subsequent stages of cognitive processing and, eventually, the patient's behavior.^{7,8} It is interesting to note that SCZ patients do not exhibit particular deficits of focused attention when task demand is constant for consecutive trials.⁹ In contrast, the goal maintenance is strongly affected in tasks in which the aim changes from trial to trial or when the main target and salient distractors are simultaneously presented.^{10–12} Within this framework, the study of early evoked potentials has provided an interesting electrophysiological marker of attention impairment in SCZ patients. Indeed, considering the visual modality, past evidence has revealed abnormalities in the P1 component, which is the first automatic evoked brain response reflecting the information flow within the extrastriate visual cortex, whose amplitude mirrors the sensory processing and the allocation of attentional resources to incoming visual stimuli.¹³ Several studies have shown that the P1 component is reduced in SCZ patients compared to healthy participants. A common characteristic of these studies is the use of simple visual stimuli, like checkerboard and abstract or degraded images.^{14–16} On the other hand, it has recently been shown that, in a spatial attention task, SCZ patients always exhibited higher

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P1 activity to foveal stimuli compared to healthy control (HC) subjects, failing to suppress their processing when asked to orient their attention to stimuli presented in the periphery of the visual field.¹⁷ Interestingly, this result is in line with the idea that early selection of task-relevant input information is a central dysfunction in SCZ.⁸

Although alterations of the attentional system are well established in SCZ, their characterization in similar psychiatric conditions is much less known. Concerning the amplitude of the P1 component, BD and SCZ patients showed lower positivity than HC.¹⁸ However, it is necessary to underline that this difference in P1 amplitude was statistically significant only considering the first visual stimulus out of the five shown in the stream included in the authors' rapid serial visual presentation task. Indeed, HC exhibited a significant decreased P1 amplitude elicited by the second to fifth stimuli with respect to P1 evoked by the first stimulus of the visual stream, thus revealing a quick habituation response during attention processing.¹⁸ Instead, both SCZ and BP patient groups showed no modulation in P1 amplitude from the first to the fifth stimulus,¹⁸ a physiological pattern that indicated that no habituation to repeated visual stimuli had occurred. Adopting a transdiagnostic approach focused on psychiatric symptoms, Bedwell and colleagues have carried out several studies on the visual P1 component. In their 2015 study, these authors found no differences in P1 amplitude among SCZ-spectrum, chronic mood disorder, and non-psychiatric control groups,¹⁹ whereas in their most recent work, they found a reduced bilateral P1 amplitude, with respect to HC, in SCZ but not in BD-I patients.²⁰ Impairments of early attentional mechanisms have also been observed in post-traumatic stress disorder.^{21,22} Attentional deficits also characterize major depressive disorder (MDD); however, these impairments mostly affect late attentional and executive mechanisms.¹⁹ Early processing of sensory input appears instead to be preserved in MDD patients, as shown by early electrocortical components related to stimulus processing, which was found to be comparable with that found in HC.^{23,24} Overall, all these findings support the idea that abnormalities in early attentional processing might reflect a shared vulnerability across different psychiatric conditions in general, and specifically within the spectrum of disorders characterized by the presence of psychotic symptomatology. The ability to discern commonalities and differences in the neurobiology of functional psychoses is limited by the different methodologies used in past studies and by the putative neurodevelopmental trajectories of each disorder. However, a definitive clarification of what SCZ, BD, and MDD have in common and in what ways they are distinct, if at all, will only be achieved from studies that examine all functional psychoses using the same study design and methodology. To contribute to this research topic, the aim of the present study was to investigate whether and how an electrophysiological index of early processing of visual stimuli (i.e., the P1 component) changes as a function of psychopathology. We used a well validated ecological paradigm, in which word pairs were visually presented while participants were engaged in a simple linguistic task (i.e., rhyme judgment). With respect to past studies on P1 using simple non-ecological stimuli, we sought to investigate this component in a more natural setting both for stimuli and task. This paradigm typically elicits a first, automatic, positive component reaching the maximum amplitude about 100 ms after stimulus onset (i.e., the P1 component), followed by the later cognitive and language-related components, which are in a domain different from that of the present study (e.g., the N150²⁵). Indeed, the P1 marks the early visual/attention stimulus processing (comparable to visual evoked potentials [VEP], used with visual stimuli like checkerboard and abstract/degraded images). In this context, that is, using word pairs as ecological stimuli, our study provides the first cross-pathological comparison of automatic visual attention processes in SCZ, BD, MDD, and HC. This allowed us to test hypotheses on the similarities/differences of cognitive alterations along the continuum represented by the major psychotic conditions. On the basis of past literature on visual P1 component, in agreement with most VEP studies (e.g., Foxe *et al.*,¹⁴ Haenschel *et al.*,¹⁵ and Butler *et al.*¹⁶),

SCZ patients were expected to exhibit reduced posterior P1 amplitude with respect to HC, whereas BD and MDD patients were expected to show P1 amplitudes greater than SCZ patients, but (not significantly) lower than HC.

Methods

Participants

Three psychiatric samples were enrolled to participate in the experiment. The first sample included 18 SCZ 'inpatients' (four women, 14 men; mean age \pm SD: 39.11 \pm 11.05 years, range 24–70 years; educational level: 10.11 \pm 2.70 years, range 7–17 years) who were recruited from the Judicial Psychiatric Hospital^a of Castiglione delle Stiviere, Mantova, Italy. These participants were included according to the following criteria: all patients were right-handed²⁶; they had been diagnosed as schizophrenic during the acute phase, on the basis of positive or negative symptoms exhibited for more than 6 months according to DSM-IV-R criteria²⁷; and at the time of the study, all patients were in a chronic state (average time from onset: 14.00 \pm 8.57 years). The diagnosis, ascertained by the psychiatrists of the ward at the time of the experiment by administering Structured Clinical Interview for DSM Disorders, classified two patients as disorganized (ICD-10 F20.1), two with paranoid/residual symptoms (F20.0/F20.5), and 14 with paranoid SCZ (F20.0). In addition, prior to the experimental session, SCZ patients were screened to assess the severity of symptoms according to the Italian version of Positive and Negative Syndrome Scale (PANSS²⁸; Table 1). Six patients were treated with typical antipsychotic drugs (i.e., chlorpromazine, clozapine, zuclopenthixol, haloperidol, and methotrimeprazine), six patients with atypical antipsychotic drugs (i.e., aripiprazole, clozapine, olanzapine, quetiapine, and risperidone), and six patients with both typical and atypical antipsychotic drugs.

Twenty BD outpatients (11 women, nine men; mean age \pm SD: 51.45 \pm 11.94 years, range 29–74 years; educational level: 14.25 \pm 3.51 years, range 5–18 years) were recruited among those followed by the Mood Disorders Outpatient Unit at the University Hospital of Padua according to the following criteria: all patients were right-handed²⁶; they had been diagnosed as bipolar (type I or II) for at least 1 year on the basis of the symptoms exhibited for more than 6 months, according to DSM-IV-R criteria²⁷; and at the time of the study, all patients were in an euthymic chronic state (average time from onset: 17.50 \pm 10.70 years). The diagnosis, ascertained by the psychiatrists of the unit at the time of the experiment by administering the MINI International Neuropsychiatric Interview,²⁹ classified six as BD-I patients, and 14 as BD-II patients. Seven patients also showed psychotic symptoms. In addition, prior to the experimental session, the comorbidity for personality disorders was excluded by administering the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II),³⁰ and all patients were screened to assess the severity of symptoms according to the Italian versions of the Hamilton Depression Rating Scale (HAM-D)³¹ and the Young Mania Rating Scale (YMRS³²; Table 1). Twelve patients were treated with atypical antipsychotic drugs (i.e., aripiprazole and quetiapine), six patients with carbolithium, 11 with SSRI antidepressant drugs (i.e., venlafaxine, escitalopram, sertraline, and fluvoxamine), four with benzodiazepines (i.e., lorazepam, lorazepam, and diazepam), and 12 patients with

^a The Judicial Psychiatric Hospital is a high-security psychiatric hospital for the criminally insane: all SCZ patients had been convicted of violent offenses and had been judged as mentally insane. Article 2046 of the Italian Civil Code and Article 85 of the Italian Penal Code exclude responsibility by reason of insanity on the premise that if there is no *mens rea* because of insanity, there is no penal responsibility. However, the guilty verdict (i.e., premeditated or unpremeditated attitude/behavior/criminal intent) is legally different from the responsibility (i.e., to be *non compos mentis*). In particular, the 'guilty but mentally ill' verdict *de facto* allows a person to be convicted for their crime but at the same time requires a psychiatric evaluation of their insanity with respect to the crime: when the psychiatric examination attests a mental disorder falling within those included in Axis I of the DSM-IV-TR, the defendant is confined in a high-security psychiatric hospital for the criminally insane. In this context, our SCZ patients are classified as 'inpatients.'

Table 1. Demographic characteristics of HC, SCZ patients, BD patients, and MDD patients, and average scores obtained for the Italian versions of the PANSS, HAM-D, and YMRS administered to ascertain patients' symptoms severity

	HC	SCZ patients	BD patients	MDD patients
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Age (years)	52.68 ± 11.88	39.11* ± 11.05	51.45 ± 11.94	53.71 ± 11.44
Sex	21 Females 9 Males	4 Females 14 Males	11 Females 9 Males	22 Females 6 Males
Education (years)	14.13 ± 3.59	10.11* ± 2.70	14.25 ± 3.51	11.21* ± 3.62
Handedness	96.92% ± 7.65%	93.05% ± 10.01%	92.12% ± 10.92	94.46% ± 8.17
Years from onset		14.00 ± 8.57	17.50 ± 10.70	15.20 ± 14.42
PANSS				
Positive symptoms				
P1 (Delusions)		4.56 ± 1.58		
P2 (Conceptual disorganization)		3.56 ± 1.29		
P3 (Hallucinatory behavior)		2.94 ± 1.63		
P4 (Excitement)		2.83 ± 1.38		
P5 (Grandiosity)		3.06 ± 1.86		
P6 (Suspiciousness/persecution)		4.11 ± 1.64		
P7 (Hostility)		2.78 ± 1.40		
Total		3.40 ± 1.65		
Negative symptoms				
N1 (Blunted affect)		4.28 ± 0.89		
N2 (Emotional withdrawal)		4.44 ± 1.04		
N3 (Poor rapport)		4.11 ± 0.83		
N4 (Passive/apathetic social withdrawal)		4.22 ± 1.17		
N5 (Difficulty in abstract thinking)		4.28 ± 1.27		
N6 (Lack of spontaneity and flow of conversation)		3.78 ± 1.00		
N7 (Stereotyped thinking)		4.28 ± 1.02		
Total		4.20 ± 1.04		
Hamilton Depression Rating Scale				
Total			4.05 ± 3.19	8.32* ± 5.17
Young Mania Rating Scale				
Total			2.00 ± 3.01	0.96 ± 1.48

**P* < 0.01 (post-hoc Tukey's HSD post-hoc test).

BD, bipolar disorder; HAM-D, Hamilton Depression Rating Scale; HC, healthy controls; MDD, major depressive disorder patients; PANSS, Positive And Negative Syndrome Scale; SCZ, schizophrenia; YMRS, Young Mania Rating Scale.

antiepileptic drugs (i.e., sodium valproate, lamotrigine, and gabapentin).

Twenty-eight outpatients suffering from MDD (22 women, six men; mean age ± SD: 53.71 ± 11.44 years, range 23–73 years; educational level: 11.21 ± 3.62 years, range 5–18 years) were recruited among those followed by the Mood Disorders Outpatient Unit at the University Hospital of Padua according to the following criteria: all patients were right-handed²⁶; they had been diagnosed as MDD patients for at least 1 year on the basis of the symptoms exhibited for more than 6 months, according to DSM-IV-R criteria²⁷; and at the time of the study, all patients were in a chronic state (average time from onset: 15.20 ± 14.42 years). The diagnosis, ascertained by the psychiatrists of the unit at the time of the experiment through the MINI International Neuropsychiatric Interview, classified all patients as MDD. In addition, prior to the experimental session, the comorbidity for personality disorders was excluded by administering the SCID-II, and all patients were screened to assess the severity of symptoms according to the Italian versions of the HAM-D and YMRS (Table 1). Six patients were treated with antipsychotic drugs (i.e., aripiprazole, quetiapine, perphenazine, and risperidone), 22 with antidepressant drugs (i.e., venlafaxine, escitalopram, citalopram,

paroxetine, duloxetine, sertraline, clomipramine, trazodone, mirtazapine, fluoxetine, nortriptyline, and amitriptyline), 10 with benzodiazepines (i.e., lorazepam, delorazepam, flurazepam, clonazepam, and alprazolam) and eight patients with antiepileptic drugs (i.e., sodium valproate, lamotrigine, and pregabalin).

The HC group consisted of 30 right-handed healthy volunteers (21 women, nine men; mean age ± SD: 52.68 ± 11.88 years, range 29–75 years; educational level: 14.13 ± 3.59 years, range 5–18 years) recruited among the healthy volunteers coming from the same region, mainly in-law relatives or friends (with no genetic links) of the patients who participated in the experiment. None of the healthy participants had been treated for any neurological or psychiatric disorder, nor were they under pharmacological treatment at the time of the experimental session. In addition, HC were briefly evaluated through the SCID-II to exclude the possibility of DSM Axis II disorders.

All participants signed their informed consent to participate in this study, which was approved by the Ethics Committee of the Department of General Psychology, Padua University Hospital and the local Ethics Committee of the Judicial Psychiatric Hospital, and were handled in accordance with the ethical standards laid down in the Declaration of Helsinki. Psychiatrists treating the patients

explained the experimental procedure to them and ensured their mental competence in understanding and reading the written informed consent to participate.

Stimuli, tasks, and procedure

Stimuli consisted of bi- or trisyllabic Italian content words (i.e., concrete object nouns, with no emotional content or valence) selected from a frequency dictionary of 5000 written Italian words, and presented in pairs on a 17" computer monitor one at a time with an interstimulus interval of 2 s; thus, the first word (W1) remained on the screen for 1 s and, after an interval of 2 s, the second word (W2, or target) appeared on the screen, until the subject responded by pressing a keyboard button, in no case longer than 5 s. Upon W2-target presentation, participants had to decide whether the word pairs rhymed. For motor responses, they used their left index or middle finger to press the keyboard buttons corresponding to match–mismatch conditions. The phonological task included 80 word pairs, 50% matches being randomly interspersed with 50% mismatch trials.

Data recording and analyses

Behavioral measures included response times and error rates to the second stimulus, and mean performance was compared between groups. Electrophysiological activity was continuously recorded in DC mode by 38 tin electrodes, 31 placed on an elastic cap according to the International 10–20 system³³; the other seven were applied below each eye (Io1, Io2), on the two external canthi (F9, F10), nasion (Nz), and mastoids (M1, M2). Amplitude resolution was 0.1 μ V; bandwidth ranged from DC to 100 Hz (6 dB/octave). Sampling rate was set at 500 Hz, and impedance kept below 5 K Ω . All cortical sites were online referred to Cz, and offline re-referenced to the average reference. Data were epoched into 2-s intervals, including 0.5 s before and 1.5 s after stimulus onset. A 100-ms baseline preceding the stimulus was subtracted from the whole trial epoch. Single trials were corrected for eye movement artifacts (i.e., vertical and horizontal movements) and blinking. To achieve this, Brain Electrical Source Analysis software (version 5.1) was used to compute ocular correction coefficients, according to Berg and Scherg.^{34,35} Each event-related potential (ERP) trial was then visually inspected for any residual artifacts, and to ensure that all trials corresponding to wrong responses were discarded: overall, 73.19% of trials were accepted for HC, 66.39% for SCZ, 74.71% for BD, and 73.85% for MDD patients, and were averaged for each group.

On the basis of mean grand-average waveforms of all groups, the first positive component (P1) was settled: the mean peak was centered on the 80–120-ms interval after word onset. Mean values of the potential measured across all participants in this temporal interval were used for statistical analysis. Examination of participants' spline maps during the P1 time window (80–120 ms) for parieto-occipital sites revealed that P7/P8 and O1/O2 electrodes had the greatest positive deflections (Fig. 1b). Thus, electrodes were clustered into two regions of interest (ROI) to perform statistics, each ROI including two electrodes: posterior left (PL: O1, P7) and posterior right (PR: O2, P8).

With regard to the behavioral measures, participants' sociodemographic data (such as age, education level, and handedness) were analyzed with separate analyses of variance (ANOVA), which included the between-subjects factor of Group (four levels: HC vs SCZ patients vs BD patients vs MDD patients). In contrast, the sex distribution among groups was analyzed with the χ^2 -test between HC and each patient group.

As differences in some sociodemographic data could influence the performance on the rhyming task, in particular by considering the accuracy, we carried out separate analyses of covariance (ANCOVA) on response times (RT) and error rates analyses, using Age and Education Level as covariate factors. In addition, in our ANCOVA, we also included the sex distribution as a between-subjects factor (two levels: Male vs Female) as this variable represents a nominal scale. All post-

hoc comparisons were computed using Tukey's honestly significant difference (HSD) test ($P < 0.05$).

On ERP data, we first carried out separate ANCOVA, using Age and Education Level as covariate factors, and the between-subjects factors of Group (four levels: HC vs SCZ patients vs BD patients vs MDD patients) and Sex (two levels: male vs female), together with the within-subjects factor of Laterality (two levels: left vs right hemisphere). As none of the sociodemographic variables revealed any significant effects on ERP data or in the overall performance of the phonological task, we carried out and reported the results from the ANOVA by including the Group and Laterality factors. Also in this case, all post-hoc comparisons were computed by means of Tukey's HSD test ($P < 0.05$).

Finally, we carried out Pearson's correlation analyses between the amplitude of P1 component in left/right posterior ROI and the performance (i.e., error rates) obtained in the phonological task of all participants included in each group. In addition, for the patient groups only, Pearson's correlation analyses were carried out between *a priori* selected PANSS scores, the total HAM-D and YMRS scores, and the P1 amplitude achieved from left/right posterior ROI to test whether specific SCZ positive symptoms – delusions (P1) and hallucinatory behavior (P3) – or the severity of depressive and mania/hypomania symptoms represented a behavioral correlate significantly linked with decreased attention filter gating.

Results

Behavioral data

As shown in Table 1, the main effect of the Age factor revealed that SCZ patients were significantly younger with respect to all other groups, $F(3, 92) = 6.86$, $P < 0.001$, $\eta^2 = 0.18$.

In addition, both SCZ and MDD patients showed lower educational levels with respect to HC and BD patients – Education factor main effect: $F(3, 92) = 8.19$, $P < 0.001$, $\eta^2 = 0.21$. No differences were found in participants' handedness, $F(3, 92) = 0.75$, NS, $\eta^2 = 0.02$. The sex distribution was significantly different in the SCZ group (larger number of male vs female participants) compared with the other groups: HC ($\chi^2(1) = 10.29$, $P < 0.001$), BD patients ($\chi^2(1) = 4.26$, $P < 0.05$), and MDD patients ($\chi^2(1) = 14.16$, $P < 0.001$). No other differences were found on sex distribution among groups. Considering the disease onset, no differences appeared among the three psychiatric samples, $F(2, 63) = 0.43$, NS, $\eta^2 = 0.01$, whereas the severity of (residual) depressive symptoms measured with the HAM-D was higher in MDD than BD patients, $F(1, 46) = 10.70$, $P < 0.01$, $\eta^2 = 0.19$ (Table 1). In any case, it is important to highlight that the severity of depressive symptoms in both MDD and BD patients was fully below the cut-off score of the HAM-D. Lastly, the YMRS mania/hypomania levels were not significant among groups, $F(1, 46) = 2.49$, NS, $\eta^2 = 0.05$.

RT showed the significant effect of education as a covariate $F(1, 86) = 6.24$, $P < 0.01$, $\eta^2 = 0.07$, and the Group \times Sex interaction, $F(3, 86) = 4.75$, $P < 0.01$, $\eta^2 = 0.14$, SCZ patients being slower than HC, BD, and MDD patients (all $P < 0.01$; Fig. 1a).

However, the ANCOVA carried out on error rates revealed no effect of age and education as covariates, $F(1, 86) = 1.01$, NS, $\eta^2 = 0.01$, and $F(1, 86) = 0.63$, NS, $\eta^2 = 0.007$, respectively, and a significant effect of the Group factor $F(3, 86) = 4.01$, $P < 0.01$, $\eta^2 = 0.12$, with SCZ and MDD patients producing more errors than HC (all $P < 0.01$; Fig. 1b). No Sex effects were found to be associated with task performance.

Electrophysiological data

Figure 2a shows the grand-mean waveforms of the first positive component (P1) in all groups in response to the first word of each pair: the mean peak was centered, depending on the group, on the 80–120-ms interval after word onset. The visual inspection of spline maps (Fig. 2b) suggested that, on both posterior ROI, SCZ had the

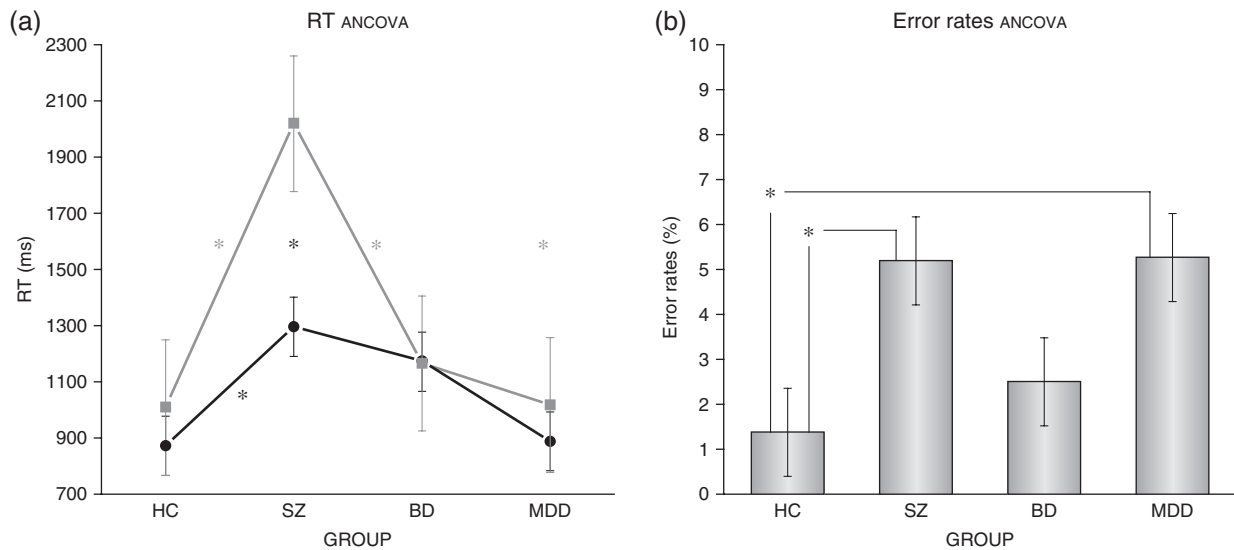


Fig. 1 Behavioral analyses carried out on (a) response times (RT) and (b) error rates to rhyming judgment task. *Significant honestly significant difference post-hoc comparisons. ANCOVA, analysis of covariance; BD, bipolar disorder patients; HC, healthy controls; MDD, major depressive disorder patients; SCZ, schizophrenia patients. (●) Male. (■) Female.

greatest P1 amplitude, as shown by the more intense red shade in the color map (Fig. 2b, red box), whereas the P1 of BD patients was the lowest in amplitude, as revealed by the light green shade in the color map (Fig. 2b, pink box). HC and MDD patients showed intermediate, yellow-orange shaded P1 amplitudes, with right and left relatively greater amplitude with respect to the homologue sites of BD patients (Fig. 2b, green and blue boxes, respectively).

The ANOVA on the P1 amplitude revealed a significant two-way Group × Laterality interaction, $F(3, 92) = 2.79, P = 0.04, \eta^2 = 0.08$, showing a bilateral pattern of P1 amplitude distribution in HC, SCZ, and MDD patients, but a greater P1 amplitude in left versus right ROI in BD patients ($P < 0.05$; Fig. 2c). With respect to group differences, SCZ patients had significant greatest P1 amplitude than HC, BD, and MDD patients (all $P < 0.01$ on left ROI and $P < 0.05$ on right ROI; Fig. 2c). No differences were found between HC and MDD patients' P1 amplitudes on both posterior ROI, whereas BD patients exhibited a significantly reduced P1 amplitude with respect to HC and MDD patients on right ROI only (all $P < 0.05$; Fig. 2c).

Pearson's correlations

Only P1 amplitude measured from posterior left ROI was positively correlated with SCZ patients' error rates and P3 symptom scales ($r(16) = 0.72, P = 0.001$ and $r(16) = 0.54, P = 0.02$, respectively). The greater the P1 amplitude in the left posterior ROI, the worse the performance in the phonological task (Fig. 3a) and the severity in the hallucinatory behavior domain (Fig. 3b).

No significant correlations were found for HC, BD and MDD patients.

Discussion

The present study examined the modulation of the early P1 component associated with automatic visual attention in HC and three groups of psychiatric patients, diagnosed with SCZ, BD, or MDD. The aim was achieved by applying the same design, procedure, and methodology to the four groups. This choice represents a crucial point of the present experimental protocol, as prior research aimed at investigating commonalities and differences in the neurobiology of functional psychoses was limited by the use of different methods and procedures, which did not allow authors to best compare SCZ, BD, and MDD patients on possible quantitative biomarkers able to distinguish disorders on some important cognitive-psychiatric variables

(e.g., see Verleger *et al.*¹⁸) using a well-validated ecological paradigm. Indeed, with respect to past studies that used simple non-natural stimuli, such as checkerboard and abstract or degraded images,^{14–16} in the present investigation we decided to adopt a more ecological setting based on word reading during a simple linguistic task, a paradigm we have used in many past investigations.^{25,36–42}

Considering the sociodemographic characteristics of psychiatric samples, SCZ patients were the younger participants, in agreement with an earlier onset of the disease with respect to both BD and MDD (DSM-5); thus, their worse performance probably relied on the severity of this psychiatric illness and/or the impact of the pharmacological treatment rather than from the age (which instead was expected to be associated with a better performance). Further, it should be noticed that all psychiatric patients were in a chronic phase of their disease, as revealed by the average time from the onset of the first episode (14.0 years for SCZ patients, 17.5 for BD, and 15.2 for MDD). With respect to education, SCZ and MDD patients showed the lowest levels, with respect to HC and BD, but this potential critical issue did not affect patients' performance on the phonological task, as error rates were minimal because they fell within 5–6%. Also, the sex bias that marked the SCZ sample (being only four females out of 18 SCZ patients) interacted with patients' RT, but again did not affect patients' performance and electrophysiological data. Therefore, the SCZ group exhibited significantly slower RT, with the women the slowest among all SCZ patients, with no effects on accuracy in task execution (error rates below 6% in all groups).

The analysis carried out on ERP data revealed different P1 amplitudes among the groups: SCZ patients showed greater P1 amplitude on posterior ROI with respect to HC. This result is inconsistent with our hypothesis (i.e., a P1 inhibited in SCZ vs HC participants).

In the literature on P1 in schizophrenics^{19,20} often the wave is computed by measuring individual peak amplitudes rather than using the mean amplitude within a time-window around the peak. However, this methodological difference does not explain our results and their discrepancy from past studies. On the contrary, it further supports the point that our results depended on the paradigm and the stimuli used. Indeed, by mathematical definition, the average amplitude in a time-window around the peak is always smaller than the peak amplitude itself. Using time-window analysis, we found greater P1 in SCZ compared with HC and the other disorders. If we used peak analysis, we would have found larger amplitudes in SCZ patients than those we have found here: the discrepancy with past studies would be greater

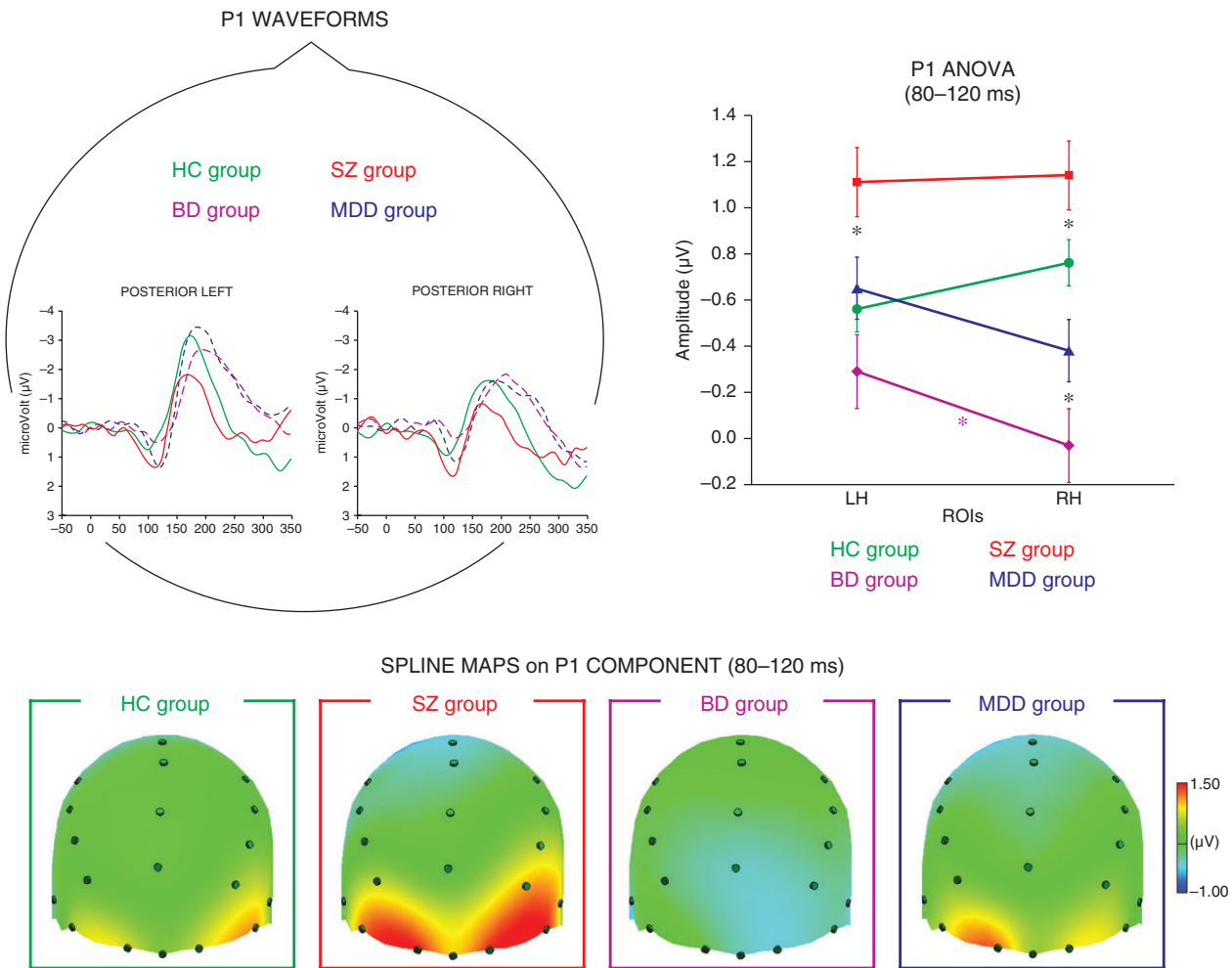


Fig.2 (a) Grand-average P1 waveforms of healthy controls (HC, green line), schizophrenia patients (SCZ, red line), bipolar disorder patients (BD, neon pink line), and major depressive disorder patients (MDD, blue line). Positivity is upward. (b) Spline maps of P1 amplitude for HC (green box), SCZ (red box), BD (neon pink box), and MDD patient (blue box). (c) Significant two-way Group × Laterality interaction. Controls' and patients' P1 amplitudes are shown for posterior left and right brain regions. *Significant Tukey's honestly significant difference post-hoc comparisons. ANOVA, analysis of variance.

not smaller. Therefore, the different method used for ERP analysis does not explain or invalidate our original result.

A credible explanation grounds on the special type of stimuli (i.e., written words) presented in our experimental paradigm for 1 s, and followed by a second word for rhyming judgment: indeed, past evidence on VEP is based on simple, abstract stimuli,^{14–16} typically presented for short temporal intervals and usually in rapid stream tasks. From this point of view, our use of ecological stimuli (i.e., simple concrete words) does not allow a straightforward comparison with past literature, due to the methodological differences. Indeed, the presentation of a word represents, in general, a complex multifaceted visual stimulus that includes a number of features (i.e., graphic, lexical, phonological, semantic, visual representation), and some of these features are more automatically extracted (e.g., the graphical and lexical ones) than others. The linguistic task allows participants to extract a specific feature out of the many possibilities. The relatively reduced P1 observed in HC may represent a controlled process aimed at extracting the task-related feature out of the many automatically generated by word presentation. Other studies on healthy adults revealed that more spread attention was associated with decreased P1 amplitude to visual stimuli (e.g., focusing attention to the heart activity induced significantly lower P1 amplitude to attentional probe stimuli).⁴³ In addition, applied to our paradigm, the automatic visual-attention processing of visual word tends to fast habituate in HC, probably to allow participants to focus on the next

linguistic stimuli with the associated phonological features. From this perspective, SCZ showed no evidence of habituation, in agreement with the Broadbent filter theory, that postulates SCZ patients have problems with early stages in serial order processing that, in turn, leads to downstream effects, such as psychotic or negative symptoms.^{44,45} As serial models have been supplanted by distributed models, the deficit may be better conceptualized in terms of resource allocation: patients cannot mobilize attentional resources and allocate them to relevant tasks. This produces an interference similar to that observed in the pre-pulse paradigm, with specific costs represented by the relative inhibition of automatic processing of P1. In the schizophrenic brain, the automatic activation of word features and the task-related process do not interfere, thus leading to an enhanced response similar to the reduced pre-pulse response found in the literature.

Interestingly, the correlation analysis carried out with both behavioral and clinical data revealed that the increased amplitude of SCZ patients' P1 component – in the posterior left ROI only – was associated with a higher number of errors in the rhyming judgment, and more severe hallucinatory symptoms (measured by the P3 subscale of the PANSS). Thus, SCZ patients with lower P1 amplitude, similar to HC, in the left hemisphere were those with a better performance and a less severe clinical picture on positive symptoms. As already suggested, the critical involvement of posterior left (rather than right) sites depends on the content of the task, in which only words were administered. In this view, an excessive automatic

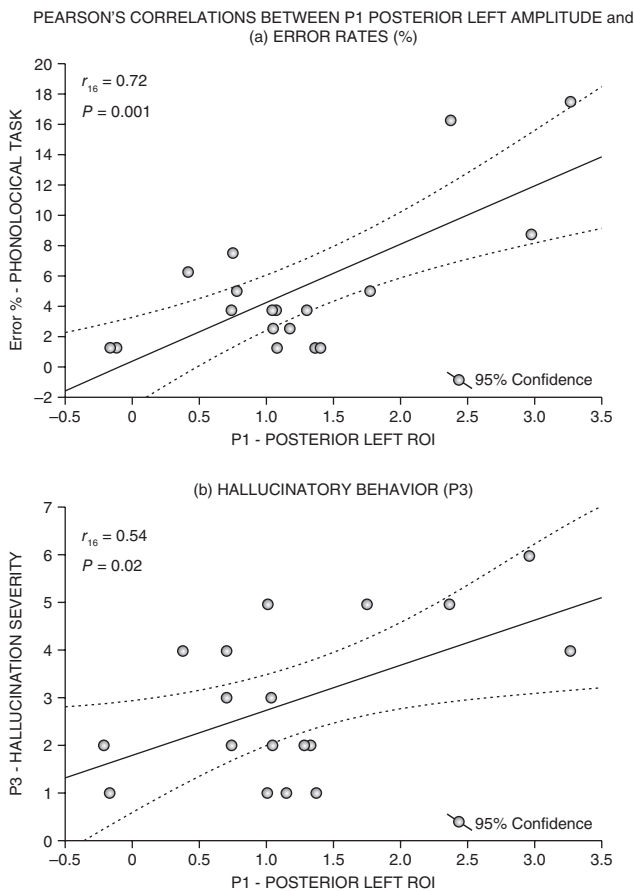


Fig.3 Pearson's correlations between P1 posterior left amplitude recorded during the phonological task in schizophrenia patients and (a) error rates to the phonological task, and (b) hallucinatory behavior construct (P3) of Positive Scale of the Positive and Negative Syndrome Scale. ROI, region of interest.

attention recruitment in the posterior left regions (larger P1) affected SCZ patients' ability to allocate it to the next relevant phases of task execution (i.e., the phonological processing of words). In line with this, in past research, the later phases of linguistic processing evidenced an impairment, namely the loss of hemispherical dominance for language⁴² that, in agreement with Crow's hypothesis,^{46,47} was found to be typically associated with more severe psychotic symptoms.⁴⁸ The strong anteroposterior asymmetry found in SCZ patients, with relatively lower anterior versus posterior activation is consistent with the well known imbalance and hypofrontality of these patients.⁴⁸

Considering the other psychiatric groups, MDD patients exhibited an electrophysiological pattern of early activation similar to that shown by HC. From the spline maps, HC and MDD patients seemed to have opposite left-right posterior asymmetry, but this was not supported by any significant statistical interaction. Instead, BD patients showed the lowest P1 amplitude on posterior ROI, in particular in the right hemisphere sites, with respect to all other groups, and their pattern of early activation was the only left-lateralized, thus revealing the involvement of a more specialized and language-related cortical network. It is worth highlighting that, at the time of the experiment, our BD participants were assessed by their psychiatrists as patients in a euthymic chronic state. In line with our interpretation on pattern of activation of HC, euthymic BD patients revealed not only the significantly lowest P1 amplitude on posterior ROI, compared with the SCZ group (but similar to P1 levels of both HC and MDD groups on posterior left ROI), but also a left-lateralized pattern of activation, thus suggesting that the automatic visual-attention processing is (at least) partially 'deteriorated' from the next, task-

related linguistic analysis. According with the meta-analysis of Chen and colleagues,⁴⁹ during cognitive tasks, euthymic BD patients consistently showed decreased activation of extrastriate visual areas, whereas inferior frontal gyrus activation was similar to that found in HC: the authors suggested that the frontal abnormalities of BD patients might be ameliorated during remission (i.e., when patients are assessed as euthymic). Therefore, the significant lower P1 amplitude on posterior ROI, in particular on right sites of our euthymic BD patients, is in agreement with the review of results provided in past meta-analysis.⁴⁹

The innovative aspect of the present research lies in the use of the same methods, instruments, and ecological procedure (with early P1 amplitude analysis) that allowed us to compare three different psychiatric samples that represent the key elements of a continuum within the psychotic spectrum disorders. Past literature on SCZ clearly showed that these patients had problems with early stages in serial order processing that led to downstream effects, marked by psychotic or negative symptoms, but the systematic study applied to other psychotic populations, such as BD and MDD, was still lacking. Our results support the view that P1 was different in the three samples of patients and this may reflect the severity of some aspects of cognitive impairment (automatic attention allocation) characterizing the three main psychiatric disorders. As expected, greater alteration in automatic visual attention was found in SCZ. Instead, reduced P1 was unexpected in BD patients, who share several features with schizophrenics, but our results can be explained in relation to the specific phase in which individuals with this disorder are when they are tested (manic, depressive, or euthymic). The euthymic BD participants showed a P1 pattern different from SCZ and from the literature on untreated patients. MDD patients revealed that, notwithstanding the many cognitive impairments described in past research in these individuals, the automatic visual processing was not affected, a result confirming the idea that, in the psychosis continuum, depression is a relatively less severe and chronic disorder (at least at a cognitive level, especially in automatic early processes).

Limitations and future directions

In conclusion, in the present study, for the first time to the best of our knowledge, we investigated P1 in MDD and euthymic BD patients and compared their responses in automatic visual attention evoked by ecological stimuli (i.e., written words) with that of SCZ patients and HC. Results of the present study may help to disentangle psychoses at a clinical level. It is known that a confusion in the diagnosis of BD in the manic phase and SCZ with positive symptoms is quite frequent (DSM-5) due to symptoms overlap. Our P1 paradigm could help, whenever a first evaluation is attempted, to carry out a more precise diagnosis between these two similar disorders. It is necessary to mention the limits of this investigation: patients were all in a chronic phase and with pharmacological treatment. Given the heterogeneity of the treatments, it is impossible to compare this variable across patients or use treatment as a covariate. Therefore, this heterogeneity represents a confound that could not be controlled. However, all patients were administered one or more drugs, so from this point of view, the sample was homogenous, and there were no patients free from drugs. It would be interesting, although difficult, to verify whether similar cross-pathology effects could be found in first-episode patients free from drugs. Of particular relevance would be the measure of P1, with this paradigm, in adolescents at risk of developing a psychosis. In a longitudinal prospective study, the finding of an enhanced P1 in individuals who will later develop SCZ would strengthen the P1 as a potential endophenotype useful for deciding early preventive intervention.

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Author contributions

A.A. and C.S. contributed to the conception and the design of the study. C.S. acquired and analyzed the data. C.S., Z.R. and A.M. drafted the manuscript and the figures, and A.A. revised the draft. All authors approved the final version of the work and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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