Objectives: Overlapping neural system dysfunctions, mainly involving the secondary somatosensory cortex (S2), the anterior cingulate cortex (ACC) and the anterior insular cortex (AIC), seem to be related to both pain-perception abnormalities and psychotic symptoms in schizophrenia (SCZ) and bipolar disorder (BD). Laser-evoked potentials (LEPs) were used to investigate pain-perception and central pain-processing abnormalities in SCZ, bipolar I disorder (BD-I), and bipolar II disorder (BD-II), and to evaluate their relationship with history of psychosis, and social-cognitive and functional impairments.

Methods: Twenty patients with SCZ, 17 patients with BD-I, and 21 patients with BD-II who were all under similar pharmacological treatment underwent clinical, functional, and neuro-psychological assessment. LEPs were analyzed in patients and 19 healthy subjects (HS). LEPs elicit responses reflecting the activity of the S2 (N1 wave) and the ACC/AIC cortices (N2/P2 complex). A four-group ANOVA was conducted between patients and HS to compare pain-perceptive thresholds (PThs), N1, and N2/P2-LEP components.

Results: Compared to HS: (i) patients with SCZ showed pain-processing and pain-perception abnormalities, as revealed by significantly higher PTh ($P<0.01$), and lower N1 ($P<0.01$) and N2/P2 ($P<0.01$) amplitudes, (ii) patients with BD-I showed only pain-processing abnormalities, as revealed by significantly lower N1 ($P<0.05$) and N2 ($P<0.01$) amplitudes; and patients with BD-II did not differ for any of the LEP variables investigated. N1 and N2 amplitudes negatively correlated to history of psychosis ($P<0.01$), social-cognition ($P<0.05$), and real-world functioning ($P<0.01$) measures in the whole group of patients.

Conclusions: To the best of our knowledge, this is the first study comparing central pain processing in patients with SCZ, BD-I, and BD-II. Our results suggest that pain-processing abnormalities may represent a novel locus of interest for research investigating trait markers of the psychosis spectrum.

Keywords
bipolar disorder, cingulate cortex, evoked potentials, insula, pain, psychosis, salience network, schizophrenia, somatosensory cortex
Abnormal pain perception has been described in patients with psychiatric disorders.\(^1^,\)\(^3\) Although most of the evidence pertains to schizophrenia (SCZ),\(^4^,\)\(^6\) pain perception has also been shown to be altered in patients with mood,\(^2^,\)\(^7\) borderline personality,\(^8\) and anxiety disorders.\(^3\) These observations suggest that pain and psychiatric disorders may be linked by one or several biological mechanisms.\(^9^,\)\(^10\)

The association between altered pain perception and psychiatric symptoms is not surprising. Studies have inferred that overlapping neurotransmitter systems (mainly serotonin, noradrenalin and dopamine)\(^11^,\)\(^12\) as well as overlapping brain networks\(^10^,\)\(^12\) may underlie both pain and psychiatric disturbances. Indeed, most, if not all, the brain regions involved in pain perception have been shown to be dysfunctional in patients with severe mental illnesses.\(^14\)

The perception of pain is thought to result from a complex interplay between many regions in the human brain, including the thalamus, anterior insular cortex (AIC), primary (S1) and secondary (S2) somatosensory cortices, anterior cingulate cortex (ACC), and prefrontal cortex (PFC).\(^15^,\)\(^16\) Despite the complex nature of this network, a rough distinction can be made between the lateral and the medial pain systems, which are thought to be predominantly involved in sensory-discriminative and affective-motivational aspects of pain, respectively.\(^17\) The key structures of the lateral pain system are the S1 and S2 which receive inputs from the lateral thalamic nuclei.\(^18^,\)\(^19\) The key structures of the medial pain system are the ACC and the AIC, which receive their major afferences from the medial thalamic nuclei.\(^18^,\)\(^19\)

Both the lateral and medial pain systems have been shown to be dysfunctional in patients with SCZ.\(^20^\)\(^\)\(^22\) Using functional magnetic resonance imaging (fMRI), De la Fuente-Sandoval and colleagues\(^20^,\)\(^21\) showed a reduced activity of the insular and cingulate cortices and an increased activity of the S1 in response to thermal painful stimuli in drug-naive patients with SCZ, when compared to healthy subjects (HS). A recent study replicated these results, also showing an interesting correlation between the reduction of insular reactivity and the magnitude of positive symptoms, suggesting that ‘insula hyporeactivity may be specifically related to psychosis.”\(^22\)

Indeed, the medial, affective-motivational ‘matrix’ of pain perception mainly relies on the activity of the AIC and ACC which, in addition to their role in pain perception, are also considered part of the so-called ‘salience network’, a neural network that functions to segregate the most relevant among internal and extrapersonal stimuli in order to guide behavior.\(^13\)

A dysfunction of this network has been related to the expression of psychotic symptoms in SCZ and BD and to impaired social-cognitive and real-world functioning abilities, which often characterize psychotic-spectrum disorders (PSDs).\(^13^,\)\(^23^,\)\(^24\) These findings are in line with evidence showing shared genetic susceptibility loci and neurocognitive impairments in SCZ and BD,\(^24\) and further support a continuum concept of psychosis rather than the Kraepeliane concept of dichotomous psychotic conditions.

Given the shared neural pathways,\(^13^,\)\(^22\) it is possible to hypothesize that pain-perception abnormalities may represent an epiphenomenon of salience circuit dysfunctions in PSDs, thus potentially being related to core features of the spectrum.

Despite the increasing amount of evidence showing an association between pain-perception abnormalities and positive symptoms in SCZ,\(^25\) no studies so far have investigated the relationship between these abnormalities and other relevant clinical outcomes in PSDs, such as social cognition and real-world functioning.

In the present study, we recorded brain potentials evoked by painful laser stimuli (laser-evoked potentials [LEPs]) to test the differences in pain perception and central pain processing in patients with SCZ, bipolar I disorder (BD-I), bipolar II disorder (BD-II), and age- and gender-matched HS.

Pain processing was assessed using latency and amplitude values of the LEP components, reflecting the activity of the sensory-discriminative (N1 wave) and affective-motivational pathways (N2-P2 complex) of the pain-perceptive system (more details are provided in Data S1).

Pain perception was assessed with the pain-perceptive thresholds (PThs), used to elicit the evoked potentials, and a Numeric Rating Scale (NRS), used to evaluate subjective pain tolerance.

We then investigated if current or past expression of psychotic symptoms in patients might be responsible for intergroup differences in pain processing as assessed by LEPs. Furthermore, in the light of the well-known association between the expression of psychotic features and poor social-cognitive and functional outcomes across diagnostic groups,\(^9\) social-cognitive and real-world functioning measures were also collected in patients with the aim of evaluating if pain-processing abnormalities might be related to these relevant clinical outcomes. In line with the continuum concept of psychosis, we expected that patients with SCZ and BD-I, who are more prone to experience psychotic relapses compared to those with BD-II, would share similar neurophysiological, cognitive, and functional abnormalities. This information could be useful to better define the blurred diagnostic and prognostic boundaries between SCZ and BD.

Based on the idea that, across the three diagnostic groups investigated (ie, SCZ, BD-I, and BD-II), altered pain-processing measures might represent a marker of psychosis proneness and impaired social-cognitive and functional abilities, the objectives of the present study were to test the following hypotheses: (i) patients with SCZ and BD-I, who are more likely to show psychotic features than those with BD-II, show altered pain processing and pain perception compared to HS, (ii) current or past expression of psychotic symptoms may be linked to similar pain-processing abnormalities in SCZ and BD-I considered as a whole group (psychosis spectrum continuum), and (iii) pain-processing abnormalities are associated with impairments in social-cognitive abilities and real-world functioning.

## Methods

### 2.1 Subjects

The Institutional Review Boards of Sapienza University of Rome approved this study. Study participants gave written and informed consent to participate. The study was conducted in accordance with the provisions of the Helsinki Declaration.
The diagnoses of SCZ, BD-I, and BD-II were confirmed with the structured clinical interview for DSM-IV. All patients were treated with a combination of one mood stabilizer (valproic acid or lithium) and one atypical antipsychotic (Table 1), according to international guidelines. Despite their name, atypical antipsychotics are widely used for acute and maintenance treatment of BD-I and BD-II, independent of the expression of psychotic symptoms. A meta-analysis of 20 randomized controlled trials assessing the relative risk for relapse in patients with BD in remission confirmed the efficacy of a number of atypical antipsychotic agents in preventing relapse to any episode vs placebo.

Patients were under stable psychotropic treatment for at least 4 wk before the LEP evaluation. Further inclusion criteria were: illness considered clinically stable by their treating physician, right handedness and competency to grant informed consent and to follow the study procedures.

We performed a systematic analysis of healthcare documentation (including outpatient and inpatient records) and data provided by relatives, care providers, and subjects to obtain information on illness duration (measured in years from the initial diagnosis of SCZ and BD), and number of previous psychotic relapses.

In patients with BD we also collected data relating to the number of previous manic, hypomanic, major depressive or mixed episodes.

Patients were excluded if they had any concomitant medical or neurological illness, current substance abuse or a history of substance dependence, a history or current comorbidity of any other Axis I disorders or borderline personality disorder, or use of psychotropic medications other than mood stabilizers and atypical antipsychotics, i.e., benzodiazepines and antidepressants.

2.2 | Clinical and neuropsychological assessment

All patients underwent clinical, functional, and neuropsychological assessments. Severity of clinical symptoms was evaluated with the Positive and Negative Syndrome Scale (PANSS). Neurocognition was investigated with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). The RBANS comprises 12 subtests that are used to calculate five index scores and a total score. Test indices are Immediate Memory, Visuospatial/Constructional, Language, Attention, and Delayed Memory. The index scores are combined to yield a total score. The total score of the Life Skills Profile-39 items (LSP-39) scale, an empirically well-tested brief functional ability outcome scale, was used to explore patients’ functioning. This score is often used as a proxy of real-world functioning in patients with SCZ and BD. Patients also completed a theory of mind task (Reading the Mind in the Eyes Test adult version [RMET]). The RMET is a forced choice mental state recognition task in which participants examine 36 black and white photos of pairs of eyes, one page for each pair of eyes. Participants select one of four words surrounding the pair of eyes, which they believe best describes what the person with those eyes is thinking or feeling. They have free access to word list definitions should they not understand a choice.

2.3 | LEPs

2.3.1 | Laser stimulation

We used an Nd:YAP (yttrium aluminium perovskite) laser stimulator under fiber-optic guidance (wavelength 1.34 mm, pulse duration 2–20 ms, maximum energy 7 J; Electronic Engineering, Florence, Italy). Laser stimuli were set to induce a clear painful pinprick (intensity 119.4–150 mJ/mm²; duration 5 ms; diameter 4 mm) and directed to the right-hand dorsum (more details are provided in Data S1). To avoid skin burns, fatigue of nociceptors, or habituation, the irradiated points were moved slightly after each stimulus, and stimuli were given at 10–30-s intervals. Subjects, wearing protective goggles, rested comfortably on a medical examination table, keeping their eyes open.

2.4 | Pain-perception measures

Pain perception was measured with the following measures: PTh and an NRS. The PTh was determined by the method of limits in two series of increasing and decreasing stimulus intensities. The laser intensity was set at 1.5 × PTh. In all sessions, subjects were asked to rate the pain evoked by laser stimuli on a 0–10 NRS (0 = no sensation, 10 = worst possible pain).

2.4.1 | Pain-processing measures

Pain-processing measures were the N1, N2, and P2 LEP Components. The different laser-evoked potential components were recorded through disk electrodes from the scalp: T3 referenced to Fz for recording the early lateralized N1 component, and Cz referenced to the nose, for recording the late vertex N2-P2 complex (pass band 0.5-50 Hz, time window 2000 ms, impedances of electrodes kept < 10 kΩ). Electro-oculographic (EOG) recordings monitored possible eye movements or blinks. No baseline correction was performed. Trials contaminated by eye-blinks and movements were removed. For each subject of the four groups of participants (20 SCZ, 17 BD-I, 21 BD-II, and 19 HS), two series of 10–15 artefact-free trials were collected and averaged off line. The N1, N2 and P2 were defined as the most negative and positive consecutive and reproducible deflections between 120 and 500 ms after stimulus onset. We measured the peak latencies and amplitudes of the lateralized N1 and the vertex N2-P2 complex. These methods adhered to the recommendations given by the International Federation of Clinical Neurophysiology.

2.5 | Data evaluation and statistical analysis

All analyses were conducted in SPSS, version 21.0 (SPSS, Inc., Chicago, IL, USA). Comparisons of demographic and clinical characteristics were performed with analysis of variance (ANOVA) for continuous variables and χ² test for categorical variables. The threshold for statistical significance was set at .05 (two-tailed, P < .05). When ANOVA determined significant between-group differences, the Bonferroni post hoc test was performed.
<table>
<thead>
<tr>
<th></th>
<th>SCZ (n = 20)</th>
<th>BD-I (n = 17)</th>
<th>BD-II (n = 21)</th>
<th>HS (n = 19)</th>
<th>ANOVA</th>
<th>χ²</th>
<th>Post hoc comparisons (Bonferroni)</th>
</tr>
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<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>SCZ vs BD-I</td>
</tr>
<tr>
<td><strong>Sociodemographic variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>39.9 (10.7)</td>
<td>41.3 (10.9)</td>
<td>41.9 (12.7)</td>
<td>37.3 (13.3)</td>
<td>0.2</td>
<td>.87</td>
<td></td>
</tr>
<tr>
<td>Sex, male, %</td>
<td>75.0</td>
<td>52.9</td>
<td>61.9</td>
<td>42.1</td>
<td>4.6</td>
<td>.20</td>
<td></td>
</tr>
<tr>
<td>Smoker, %</td>
<td>45.0</td>
<td>52.9</td>
<td>47.6</td>
<td>31.6</td>
<td>1.8</td>
<td>.60</td>
<td></td>
</tr>
<tr>
<td>Education, years, mean (SD)</td>
<td>12.4 (1.7)</td>
<td>12.7 (1.8)</td>
<td>13.5 (2.4)</td>
<td>13.8 (2.6)</td>
<td>2.0</td>
<td>.11</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical variables, mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of illness onset, years</td>
<td>24.7 (6.0)</td>
<td>27.1 (7.3)</td>
<td>28.2 (7.7)</td>
<td></td>
<td>1.3</td>
<td>.28</td>
<td></td>
</tr>
<tr>
<td>Duration of illness, years</td>
<td>15.4 (8.2)</td>
<td>14.2 (6.5)</td>
<td>13.7 (6.4)</td>
<td></td>
<td>0.3</td>
<td>.75</td>
<td></td>
</tr>
<tr>
<td>No. of previous major depressive episodes</td>
<td>1.7 (0.8)</td>
<td>1.8 (0.8)</td>
<td></td>
<td></td>
<td>0.3</td>
<td>.57</td>
<td></td>
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<tr>
<td>No. of previous manic episodes</td>
<td>2.0 (0.6)</td>
<td>1.7 (1.3)</td>
<td></td>
<td></td>
<td>0.3</td>
<td>.58</td>
<td></td>
</tr>
<tr>
<td>No. of previous hypomanic episodes</td>
<td>2.0 (1.4)</td>
<td>2.9 (1.5)</td>
<td></td>
<td></td>
<td>0.7</td>
<td>.40</td>
<td></td>
</tr>
<tr>
<td>No. of previous mixed episodes</td>
<td>0.8 (0.6)</td>
<td>0.3 (0.5)</td>
<td></td>
<td></td>
<td>3.1</td>
<td>.01</td>
<td></td>
</tr>
<tr>
<td>No. of previous psychotic episode</td>
<td>3.6 (1.7)</td>
<td>2.2 (0.8)</td>
<td></td>
<td></td>
<td>15.6</td>
<td>&lt;.01</td>
<td></td>
</tr>
<tr>
<td>PANSS Positive Subscale score</td>
<td>17.0 (5.5)</td>
<td>15.2 (4.2)</td>
<td>14.3 (6.0)</td>
<td></td>
<td>1.2</td>
<td>.30</td>
<td></td>
</tr>
<tr>
<td>PANSS Negative Subscale score</td>
<td>19.7 (4.5)</td>
<td>14.6 (6.6)</td>
<td>14.7 (7.2)</td>
<td></td>
<td>9.6</td>
<td>&lt;.01</td>
<td></td>
</tr>
<tr>
<td>PANSS General Subscale score</td>
<td>36.7 (8.4)</td>
<td>30.7 (4.2)</td>
<td>32.5 (8.9)</td>
<td></td>
<td>2.9</td>
<td>.11</td>
<td></td>
</tr>
<tr>
<td>Anxiety sub-item (G2) of PANSS</td>
<td>2.5 (1.3)</td>
<td>2.1 (1.1)</td>
<td>2.4 (1.4)</td>
<td></td>
<td>0.6</td>
<td>.53</td>
<td></td>
</tr>
<tr>
<td>Depression sub-item (G6) of PANSS</td>
<td>2.5 (1.5)</td>
<td>2.6 (1.3)</td>
<td>3.1 (1.4)</td>
<td></td>
<td>0.9</td>
<td>.41</td>
<td></td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotic plus valproate, n</td>
<td>20</td>
<td>17</td>
<td>19</td>
<td></td>
<td>3.6</td>
<td>.16</td>
<td></td>
</tr>
<tr>
<td>Antipsychotic plus lithium, n</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td></td>
<td>3.6</td>
<td>.16</td>
<td></td>
</tr>
<tr>
<td>Risperidone, n</td>
<td>16</td>
<td>15</td>
<td>13</td>
<td></td>
<td>3.8</td>
<td>.15</td>
<td></td>
</tr>
<tr>
<td>Quetiapine, n</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td></td>
<td>1.9</td>
<td>.38</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole, n</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
<td>1.8</td>
<td>.41</td>
<td></td>
</tr>
<tr>
<td>Olanzapine, n</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td></td>
<td>2.8</td>
<td>.32</td>
<td></td>
</tr>
<tr>
<td>Valproate dose, mg, mean (SD)</td>
<td>1540.0 (507.9)</td>
<td>1408.8 (640.9)</td>
<td>1471 (486.6)</td>
<td></td>
<td>0.6</td>
<td>.94</td>
<td></td>
</tr>
<tr>
<td>Lithium dose, mg, mean (SD)</td>
<td>1050.0 (212.13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total antipsychotic dose, mg, mean (SD)</td>
<td>172.5 (34.3)</td>
<td>167.6 (63.6)</td>
<td>165.9 (85.9)</td>
<td></td>
<td>0.6</td>
<td>.94</td>
<td></td>
</tr>
</tbody>
</table>

HS, healthy subjects; SD, standard deviation; PANSS, Positive and Negative Syndrome Scale.

*Chlorpromazine equivalents.
Normality was assessed by the Shapiro–Wilk test. Measures of N2 amplitude, the RBANS language and visuospatial indices were non-normally distributed, and thus they were transformed using their natural logarithms prior to statistical analyses with parametric methods. N2 amplitude was not normally distributed after this, and therefore we transformed it into normality using square root.

Based on the existing evidence mentioned in the Introduction, a priori hypothesis-driven Pearson correlations were performed to evaluate the relationship of LEP measures with (i) current or past expression of psychotic symptoms (i.e., PANSS Positive Symptoms total score and number of previous psychotic episodes), (ii) the RMET score, as a measure of social-cognitive ability, and (iii) the LSP-39 total score, as a proxy of real-world functioning.

Standard methods to adjust the $P$-values of multiple correlation coefficients, such as the Bonferroni and Sidak methods, are generally considered too conservative. According to some authors, one of the best approaches for dealing with this situation is to conduct a permutation (or resampling test). Bootstrap resampling with replacement ($B = 10,000$ bootstrap samples) was thus used to validate the findings obtained using correlation analyses. Bootstrapping involved randomly sampling the data with replacement ($B = 10,000$ bootstrap samples) and repeating the correlation analyses to assess the accuracy of the confidence intervals.

Prior literature has suggested that age, gender, and use of psychotropic drugs can influence the amplitude and latency of evoked potentials. Therefore, we employed additional extended models using age, gender, chlorpromazine (CPZ) equivalents, lithium doses, and valproic acid doses as covariates in both intergroup comparisons and correlation analyses.

One of the main hypotheses of the study was to assess the relationship between LEPs and psychotic features; therefore, in order to address potential confounding factors associated with the course of illness, when possible we employed further extended models using the following clinical variables as covariates: duration of illness, severity of anxiety or depression symptoms (sub-items of the PANSS General Subscale) and number of previous manic, hypomanic or depressive episodes.

## RESULTS

### 3.1 | Subjects

Twenty patients with SCZ, 17 patients with BD-I, 21 patients with BD-II, and 19 HS fitted the inclusion criteria and completed all the procedures in the study.

Subjects with a history of psychiatric illness other than SCZ and BD were excluded.

No differences between the four groups were found in age, sex, education, and smoking status. No differences between the three groups of patients were found in medications, duration of illness, age of illness onset, the PANSS General Subscale and its two sub-items Depression and Anxiety (Table 1). All patients in the BD-I group, but none in the BD-II group, had experienced at least one psychotic episode.

Patients with SCZ had a significantly higher number of psychotic relapses compared to BD-I ($P < .01$) and higher scores on the PANSS Negative Symptoms Subscale compared to both BD-I ($P < .01$) and BD-II ($P < .01$). Patients with BD-I and BD-II did not significantly differ in terms of previous manic, depressive and mixed episodes (Table 1). Patients with SCZ performed significantly worse in the neurocognitive, social-cognitive, and functioning domains compared to both BD-I and BD-II. The latter group showed significantly better scores than BD-I in the neurocognitive domain, as assessed with the RBANS. No significant differences were found in the RMET and the LSP-39 total scores between BD-I and BD-II (main group effects and results of post hoc tests are given in Table 2).

### Table 2 Total and index scores of the RBANS, and the total score in the RMET and Life Skill Profile-39 in patients with schizophrenia (SCZ), bipolar I disorder (BD-I), and bipolar II disorder (BD-II)

<table>
<thead>
<tr>
<th></th>
<th>SCZ (n = 20)</th>
<th>BD-I (n = 17)</th>
<th>BD-II (n = 21)</th>
<th>ANOVA</th>
<th>Post hoc comparison values (Bonferroni)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$F$</td>
<td>$P$-value</td>
</tr>
<tr>
<td>RBANS, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>78.9 (8.2)</td>
<td>86.1 (5.4)</td>
<td>90.9 (6.3)</td>
<td>19.1</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Attention index</td>
<td>79.1 (7.7)</td>
<td>83.3 (5.3)</td>
<td>88.4 (9.4)</td>
<td>7.2</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Language index</td>
<td>84.1 (7.2)</td>
<td>88.2 (6.2)</td>
<td>92.3 (7.2)</td>
<td>7.2</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Immediate memory index</td>
<td>76.1 (8.8)</td>
<td>82.0 (6.4)</td>
<td>88.6 (10.4)</td>
<td>10.7</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Delayed-memory index</td>
<td>75.5 (8.9)</td>
<td>81.6 (4.4)</td>
<td>89.9 (7.8)</td>
<td>20.5</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Visuospatial/constructional index</td>
<td>80.8 (8.3)</td>
<td>86.2 (7.1)</td>
<td>94.5 (8.5)</td>
<td>15.3</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>RMET</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total, mean (SD)</td>
<td>19.7 (4.6)</td>
<td>27.0 (4.5)</td>
<td>27.4 (4.9)</td>
<td>16.5</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Life Skill Profile-39</td>
<td>103.4 (19.9)</td>
<td>91 (17.4)</td>
<td>79.8 (15.2)</td>
<td>9.2</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; RMET, Reading the Mind in the Eyes test; SD, standard deviation.
3.2 | Comparison of LEPs between groups

A four-group ANOVA was conducted between SCZ, BD-I, BD-II and HS. Mean and standard deviation values for PTh, NRS, N1, N2 and P2 amplitudes and latencies are given in Table 3.

3.3 | Pain perception

We found a significant group effect for PTh \[F(3, 76) = 3.0, P < .05\] that was accounted for by significant differences between SCZ and HS (\(P < .01\)), and between SCZ and BD-II (\(P < .05\)). A significant group effect was found for NRS \[F(3, 76) = 4.3, P < .01\] that was accounted for by significant differences between SCZ and HS (\(P < .01\)), and between SCZ and BD-II (\(P < .05\)).

3.4 | Pain processing

No significant group effect was found for N1, N2 and P2 latency values.

There was a significant group effect for the N1 amplitude \[F(3, 76) = 6.6, P < .01\] that was accounted for by significant differences between SCZ and HS (\(P < .01\)) and between BD-I and HS (\(P < .01\)).

There was a significant group effect for the N2 amplitude \[F(3, 76) = 20.3, P < .01\] that was accounted for by significant differences between SCZ and HS (\(P < .01\)), and between SCZ and BD-II (\(P < .01\)); a value near the threshold of significance was found in N2 for group differences between SCZ and BD-I (\(P = .052\)), and between BD-I and BD-II (\(P = .051\)).

In the extended models, in which the potential confounding variables were added as covariates, the significance of these results did not change (see Data S1).

3.5 | A priori hypothesis-driven correlation analyses: pain processing, current expression of psychotic symptoms, history of psychosis, and social-cognitive and functional outcomes

Across the three groups of patients, both the RMET and the LSP-39 total score were significantly correlated with the N2 amplitude \([r(56) = .32, P < .05; \text{and } r(56) = -.36, P < .01\]) respectively, with lower scores in the RMET (indicating worse social cognitive abilities) corresponding to lower N2 amplitudes, whereas higher scores in the LSP-39 total score (indicating lower levels of real-world functioning) corresponded to lower N2 amplitudes.

Across only those patients with a lifetime history of psychosis (SCZ and BD-I), we found that the number of previous psychotic episodes was negatively correlated with P2 \([r(35) = -.047, P < .01]\) and N2 \([r(37) = -.58, P < .01]\) amplitudes, such that a higher number of psychotic episodes corresponded to lower N2 and P2 amplitudes.

The results of the bootstrap analyses supported the findings of the original analyses (see also Data S1).

### Table 3

Mean and standard deviation (SD) values for pain processing (N1, N2 and P2 amplitudes (amp) and latency (lat)) and perception (PTh and NRS) in patients with schizophrenia (SCZ), bipolar I disorder (BD-I), and bipolar II disorder (BD-II) across the four groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>SCZ (n = 20)</th>
<th>BD-I (n = 17)</th>
<th>BD-II (n = 21)</th>
<th>HS (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTh (mJ/mm²)</td>
<td>76.4 (21.1)</td>
<td>63.5 (21.4)</td>
<td>60.2 (23.9)</td>
<td>62.6 (18.9)</td>
</tr>
<tr>
<td>NRS</td>
<td>3.5 (2.1)</td>
<td>5.0 (2.7)</td>
<td>5.8 (3.0)</td>
<td>6.0 (1.3)</td>
</tr>
<tr>
<td>PTh (μV)</td>
<td>7.5 (7.1)</td>
<td>12.6 (4.8)</td>
<td>15.6 (8.9)</td>
<td>17.8 (7.8)</td>
</tr>
<tr>
<td>PTh (ms)</td>
<td>330.2 (46.8)</td>
<td>348.1 (22.2)</td>
<td>359.3 (28.6)</td>
<td>342.7 (27.2)</td>
</tr>
<tr>
<td>PTh (mV)</td>
<td>4.0 (1.9)</td>
<td>5.8 (4.6)</td>
<td>6.2 (4.8)</td>
<td>6.2 (4.8)</td>
</tr>
<tr>
<td>PTh (ms)</td>
<td>195.5 (71.5)</td>
<td>140 (79.4)</td>
<td>158 (56.6)</td>
<td>158 (56.6)</td>
</tr>
<tr>
<td>PTh (mV)</td>
<td>3.6 (4.2)</td>
<td>9.7 (3.3)</td>
<td>20 (15.6)</td>
<td>20 (15.6)</td>
</tr>
<tr>
<td>PTh (ms)</td>
<td>210.0 (23.7)</td>
<td>221.4 (20.3)</td>
<td>223.14 (20.9)</td>
<td>221.0 (15.1)</td>
</tr>
<tr>
<td>N1 amp (μV)</td>
<td>4.0 (1.9)</td>
<td>5.8 (4.6)</td>
<td>6.2 (4.8)</td>
<td>6.2 (4.8)</td>
</tr>
<tr>
<td>N1 lat (ms)</td>
<td>195.5 (71.5)</td>
<td>140 (79.4)</td>
<td>158 (56.6)</td>
<td>158 (56.6)</td>
</tr>
<tr>
<td>N2 amp (μV)</td>
<td>3.6 (4.2)</td>
<td>9.7 (3.3)</td>
<td>20 (15.6)</td>
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</tr>
</tbody>
</table>

Amplitude of laser-evoked potentials was measured in microvolts (μV) and latency in milliseconds (ms). Pain threshold was measured in mJ/mm². HS, healthy subjects; PTh, pain threshold; NRS, Numeric Rating Scale.
Based on the observation of shared neural system dysfunctions in SCZ and BD in brain areas typically associated with both central processing of painful stimuli and expression of psychosis, we hypothesized that pain-processing abnormalities in these disorders might be related to core clinical features of PSDs.

To the best of our knowledge, this is the first study: (i) to compare central pain-processing abnormalities in patients with SCZ, BD-I, and BD-II, and (ii) to investigate the relationship of these abnormalities with relevant clinical features of the psychosis spectrum, such as the number of previous psychotic episodes, social cognition, and real-world functioning.

Hypothesis 1 Patients with SCZ and BD-I, but not BD-II, show altered pain processing and pain perception compared to HS

The first objective of the study was to test the hypothesis that patients with SCZ and BD-I, who are more likely to show psychotic features than those with BD-II, show altered pain processing and pain perception compared to HS.

When compared to HS, patients with SCZ showed both pain-perception and pain-processing abnormalities, as revealed by: (i) higher pain-perceptive thresholds, (ii) reduced pain sensitivity, as revealed by the lower NRS scores, and (iii) reduced amplitudes of the sensory-discriminative (N1) and the affective-motivational (N2-P2) LEP components.

When compared to HS, the BD-I group showed only pain-processing abnormalities, i.e., a reduced activity of the sensory-discriminative pain-processing pathway (N1) and ‘moderate’ dysfunctions in the affective-motivational pathway (N2-P2) in response to noxious stimuli; the N2 component, in fact, showed significantly lower amplitude values compared to HS, although these values were not as low as those observed in SCZ. None of the BD-I pain-perceptive measures differed from those observed in HS.

Finally, the BD-II and HS groups showed comparable pain-perceptive and pain-processing values (Table 3 and Figure 1).

The finding of a reduced N1 amplitude in SCZ and BD-I suggests a reduced S2 activation in response to painful stimuli. Admittedly, LEPs have a limited spatial resolution and some authors suggest that S1 also contributes to the generation of N1 and a reduced activation of S1 may attenuate N1.41

The S1/S2 are crucial in higher order somatosensory perception, including somatosensory-specific attention, learning, integration, discrimination, and memory.42,43

The altered activation of S1/S2 suggests that somatosensory stimuli might be processed in a less anatomically specialized manner in psychotic spectrum disorders compared to controls.20,21,44 However, given the findings of reduced N2/P2 amplitude and pain perception in our SCZ and—at least to some extent—BD-I samples, an alternative explanation could be that the sensory input that reached the somatosensory areas may be reduced (e.g., through a top-down modulation) in these patients, thus resulting in reduced N1 amplitudes.45,46

Altered activation of somatosensory areas in response to painful stimuli in SCZ has been found in two recent studies showing increased S1 activation in response to painful stimuli in patients with SCZ.20,21 Patients with SCZ show reduced interaction between primary sensorimotor areas, such as S1, and higher order somatosensory areas, such as S2, when processing somatosensory stimuli.47-49 The abnormal cross-talk between S1 and S2 seems to be characterized by a hyper-activation of the former and a hypo-activation of the latter, as shown by a recent magnetoencephalography (MEG) study.49 According to some preliminary evidence, this abnormal cross-talk and the reduced S1–S2 synchronization might represent a trans-diagnostic trait marker of PSDs;5,20,21 providing an interesting potential explanation for N1 amplitude reductions in our SCZ and BD-I groups. Indeed, all patients in the BD-I group experienced at least one psychotic episode. Furthermore, similar N1 amplitude values were found in BD-II and HS. Taken together, these findings suggest that the trans-diagnostic expression of psychotic features, rather than the BD diagnosis per se, is more likely responsible for the expression of similar N1 abnormalities in BD-I and SCZ.

The affective motivational pathway (N2-P2 components) showed processing abnormalities in both the SCZ and BD-I groups. However, only the N2 component, and to a lesser extent compared to SCZ, seemed to be affected in BD-I.

The N2-P2 biphasic complex is thought to reflect the activity of the insular and cingulate cortices, in response to the laser noxious stimuli.31 The reduced amplitudes of the components of this complex observed in our SCZ group are in line with recent neuroimaging studies showing diminished insular and cingulate cortex responses to thermal pain in patients with SCZ.20-22

Patients with BD-I showed only a partial impairment of the affective-motivational pain-processing pathway, consistent with a large body of evidence suggesting similar, but smaller, salience circuit dysfunctions in BD-I compared to SCZ.50-53 The affective motivational pathway is thought to process the unpleasant character of the pain
experience.\textsuperscript{17,54} The partial integrity of this pathway in BD-I could thus provide an explanation for the absence of pain-perceptive abnormalities in this group of patients.

As for the N1 component, the lack of differences between BD-II and HS in the N2-P2 LEP component further suggests that pain-processing abnormalities are mainly led by the expression of psychosis-spectrum features rather than the BD diagnosis.

These findings are line with recent evidence identifying common neurophysiologic\textsuperscript{55,56} and neurobiological markers\textsuperscript{13} intrinsic to psychosis across diagnostic boundaries.\textsuperscript{24,57,58}

No differences were found between HS and the three groups of patients in any of the LEP latency values. In any evoked potential recordings, owing to spatial-temporal summation, if the amplitude is reduced the latency is expected to increase accordingly. In LEP studies, however, changes in amplitude are far more marked than those in latency.\textsuperscript{59} Nevertheless, we cannot exclude the possibility that the two measures may dissociate when there is no deficit in the nociceptive pathways and only the excitability of central generators has changed.

**Hypothesis 2** Current or past expression of psychotic symptoms may be linked to similar pain-processing abnormalities in SCZ and BD-I

The second objective of the study was to test the hypothesis that current or past expression of psychotic symptoms may be linked to similar pain-processing abnormalities in SCZ and BD-I. Amplitudes of both the N2 and P2 LEP components were negatively correlated with numbers of previous psychotic episodes in SCZ and BD-I, while no correlations were found with current expression of positive symptoms in the whole group of patients.

As mentioned in the Introduction, evidence suggesting a neural network overlap between the affective-motivational pathway of pain processing and the salience network\textsuperscript{13,20-22} may provide an interesting explanation for this finding.

There is literature showing a link between the occurrence of psychotic episodes and functional and structural abnormalities of the AIC and the ACC, core regions of both the affective-motivational pain pathway\textsuperscript{20-22} and the salience network.\textsuperscript{13, 50} A head-to-head comparison of voxel-based morphometry studies revealed that AIC and ACC lesions are common among individuals with BD-I and SCZ.\textsuperscript{50} Interestingly, the extent of these lesions and the functionality of these brain regions in BD-I seem to be linked to the course of illness and to the occurrence of psychotic episodes (but not to current expression of positive symptoms), such that a higher number of psychotic episodes corresponds to greater network dysfunctions.\textsuperscript{60-63} These observations suggest that pain-processing abnormalities observed in our BD-I and SCZ groups may represent trait rather than state markers of the psychosis spectrum, providing a potential explanation for the absence of correlations between the LEP components and severity of positive symptoms. One hypothesis is that the mild pain-processing abnormalities observed in the affective motivational pathway of BD-I, reflecting a moderate dysfunction of the salience network compared to SCZ, could be associated with a less severe course of illness, characterized by a lower number of psychosis relapses and mild cognitive and functioning deterioration.

It has to be noted that the absence of a significant association between current expression of positive symptoms and central pain-processing measures is in contrast with the findings of a study by Linnman et al.\textsuperscript{22} These authors found a negative association between the magnitude of positive symptoms and reactivity of the insula to electric aversive stimuli in 15 patients with SCZ.\textsuperscript{22} Differences in sample size, methodology (fMRI vs LEPs), and clinical characteristics (age and duration of illness) of patients may provide an explanation for this discrepancy. As mentioned above, evidence suggests that state/transient markers of PSDs (e.g., severity of symptoms) are less likely associated with stable neurophysiological dysfunctions than state markers (e.g., history of psychosis).\textsuperscript{13,50,57} Given the younger age and shorter duration of illness of the sample enrolled by Linnman and colleagues, it is possible to hypothesize that in their study the observed neurophysiological dysfunctions were more subtle and thus more susceptible to changes in state/transient variables, such as the magnitude of positive symptoms. Unfortunately, Linnman and colleagues did not report the number of previous psychotic relapses for their sample, making it difficult to perform a straight comparison with our results. Thus, these considerations are only speculative and more studies are needed to clarify the impact of state/transient vs trait markers of PSDs on central pain-processing measures.

**Hypothesis 3** Pain-processing abnormalities are associated with impairments in social-cognitive ability and real-world functioning.

In line with this hypothesis, we found that lower N2 amplitude values, suggesting AIC hypo-activity, were significantly correlated with social-cognitive and real-world functioning impairments in the whole group of patients.

Of course, these considerations are only speculative, given the small sample size and absence of corrections for multiple comparisons, but they might still be of relevance as hypothesis-generating findings.

The AIC is regarded as a fundamental substrate of emotional experience and social cognition\textsuperscript{23,64}; the impaired ability to infer mental states in others and consequently difficulty in understanding social keys may have a large relevance in the day-to-day life of patients, thus providing an explanation for our findings for functional outcomes.

If these results are confirmed in a larger sample of patients, the identification of pain-processing abnormalities in SCZ and BD may become a novel and economically accessible trans-diagnostic target for future research on biomarkers of psychosis proneness and functional deterioration.

Although limited by the cross-sectional design, our study suggests that LEPs may potentially be helpful to identify those patients with BD with a more severe course of illness, more likely having a higher number of psychosis episodes and worse social-cognitive and real-world functioning abilities.

Future studies with larger samples and a longitudinal design are needed to draw definitive conclusions.
4.1 Limitations and strengths

Limitations of the study include the rather small sample size and the cross-sectional design.

Also, if we assume that there is intensified antipsychotic treatment during psychotic exacerbations and that antipsychotic agents may exert neurotoxic effects, then the finding of a negative correlation between the number of previous psychotic episodes and the N2-P2 complex amplitudes may potentially be the result of prolonged/intense antipsychotic treatment.\(^6\) However, duration of illness did not correlate with any of the LEP measures, making unlikely the hypothesis that prolonged treatment may affect pain-processing and pain-perceptive measures, and in line with results from a recent meta-analysis.\(^6\)

Another limitation is the absence of corrections for multiple comparisons in the correlation analyses. However, literature suggests that: ‘simply describing what tests of significance have been performed, and why, is generally the best way of dealing with multiple comparisons,’ while Bonferroni corrections usually result in a loss of statistical power.\(^6\) Furthermore, correlations between LEP component, functional outcome, and number of previous psychotic episodes remained significant even using a less liberal level of significance (i.e., \(P<.01\)).

Finally, the use of LEPs to investigate pain-processing abnormalities in patients with SCZ and BD may have some limitations and caution needs to be taken in interpretations of our results. We cannot exclude that the abnormalities in LEP components (i.e., N1, N2, and P2) may also reflect, rather than a specific alteration in central pain-processing, an aspecific dysfunction of salience processing.\(^6\)

The main strength of the study is that most of the potential confounding factors reported in previous published papers investigating pain perception in psychiatric disorders have been taken into consideration:

- Previous literature suggests that the severity of depressive and anxiety symptoms may increase sensibility to pain; however: (i) no correlations were found between the depression and the anxiety sub-items of the PANSS General Subscale and any of the pain-perceptive or pain-processing measures, and (ii) adjusting the inter-group and correlation analyses for the depression and the anxiety sub-items of the PANSS general subscale did not change the significance of the results.

- There is evidence suggesting that psychotropic drugs could be responsible for pain-perception abnormalities; however: (i) the BD-II group, who were on a psychopharmacological treatment comparable to that of the SCZ and BD-I groups, did not show any pain-perceptive or pain-processing abnormalities, (ii) no correlations were found between CPZ equivalent, valproic acid and lithium doses and any of the pain-perceptive or pain-processing measures, and (iii) adjusting the inter-group comparisons for the medication variables did not change the significance of the results. Our results are thus in line with recent observations of the absence of analgesic properties of psychiatric drugs.\(^3\)

- The effect of ‘course of illness’ variables other than history of psychosis has been taken into account. Indeed, adjusting the inter-group and correlation analyses for each ‘course of illness’ variable did not change the significance of the results.

5 CONCLUSIONS

Patients with SCZ showed pain-perceptive and pain-processing abnormalities in both the sensory-discriminative and affective-motivational pathways. With regard to BD patients, when we compared their results to those for SCZ, we found a moderate profile of pain-processing abnormalities only in the BD-I subgroup, with impairments involving the sensory-discriminative pathway but only to a small extent the affective-motivational pathway; also, no pain-perceptual abnormalities were found in this group. On the other hand, in the patients in the BD-II subgroup we found that pain-processing and pain-perceptive values were comparable to those of HS.

Our study suggests that in patients with SCZ and BD-I the reduced ability to process pain stimuli could be a trait marker of psychosis proneness in the presence of an established functional and cognitive deterioration. If these results are confirmed, pain-processing measures could represent a novel locus of interest for the study of psychotic illness, and LEPs could represent an intriguing new neurobiological trans-diagnostic marker of psychotic proneness and poor functional and cognitive outcomes.

DISCLOSURES

The authors of this paper do not have any commercial associations that might pose a conflict of interest in connection with this manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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