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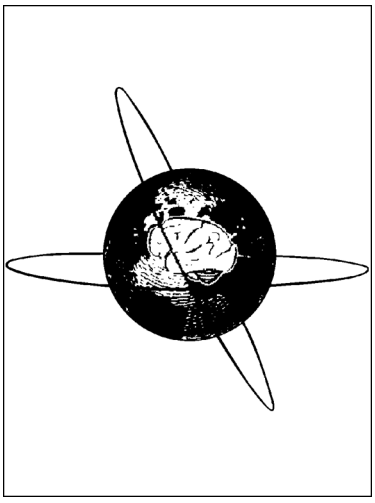

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Investigating visuo-tactile mirror properties in Borderline Personality Disorder: a TMS-EEG study

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Highlights

- Patients with borderline personality disorder (pw-BPD) show reduced levels of cognitive empathy.
- Pw-BPD exhibited lower behavioral performance in touch localization during the processing of visual stimuli showing touches.
- Physiological results show alterations within the somatosensory network during touch observation and touch perception in pw-BPD.

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Declarations of interest

None.

Abstract

Objectives: Patients with borderline personality disorder (pw-BPD) have decreased levels of cognitive empathy, which may be subtended by mirror-like mechanisms in the somatosensory cortices, i.e., the Tactile Mirror System (TaMS). Here, we aimed to shed light on the TaMS and empathic deficits in pw-BPD focusing on connectivity, using transcranial magnetic stimulation and electroencephalography (TMS-EEG).

Methods: After study preregistration, we collected self-report measures of empathic abilities, behavioral performance in a visuo-tactile spatial congruency task investigating TaMS activity, and TMS-evoked potentials (TEPs) from 20 pw-BPD and 20 healthy controls. TMS was delivered over the right primary somatosensory cortex (S1) during touch observation and real touch delivery.

Results: Pw-BPD reported significantly lower levels of cognitive empathy than controls and made significantly more errors in reporting the side of real touches during touch observation. Moreover, pw-BPD presented an altered connectivity pattern from S1-TEPs during touch perception and touch observation, in the last case without differences between human- and object-directed touches.

Conclusions: The results do not support a specific impairment of TaMS in pw-BPD, but reveal significant behavioral and connectivity alterations within the somatosensory network during touch processing.

Significance: The present findings temper the proposed role of the TaMS in BPD, while still highlighting the involvement of somatosensory network alterations.

Keywords

empathy, cross-modal integration, TMS-evoked potentials, tactile mirror system, psychiatric disorders, preregistered

1. Introduction

Borderline personality disorder (BPD) is a psychiatric condition characterized by difficulties in emotional and behavioral regulation, issues with self-image, and alterations in interpersonal relationships. Many of these symptoms can be attributed to deficits in social cognition, including difficulties with mentalization and empathy (Lazarus et al. 2014; Sosic-Vasic et al. 2019), which are recognized as one of the core features of the disease (D'Abate et al. 2020). Specifically, patients with BPD (pw-BPD) exhibit reduced levels of cognitive empathy compared to healthy individuals. This suggests challenges in understanding others' perspectives, whereas the affective dimension (i.e., sensing others' feelings) shows unaltered or even increased levels (Grzegorzewski et al., 2019; Harari et al., 2010; Martin et al., 2017). Given the essential role of empathy in social connections, it is imperative to understand the cognitive and neurophysiological underpinnings of this impairment.

Empathic responses are linked to the activity of mirror neuron system. From this perspective, an understanding of others' actions and sensations as well as intentions and emotions occurs through automatic simulation processes (Keysers and Gazzola, 2009). From the original discovery of mirror neurons in the monkey's ventral premotor area (di Pellegrino et al., 1992; Gallese et al., 1996), analogous mirror-like mechanisms have been described in humans in the motor (Barchiesi and Cattaneo, 2015; Buccino et al., 2004; Catmur et al., 2007; Ubaldi et al., 2015) and in the somatosensory domain (Blakemore et al., 2005; Schaefer et al., 2009). In the Tactile Mirror System (TaMS), the same cortical areas involved in tactile perception are activated during the observation of others being touched (Keysers et al., 2010; Pihko et al., 2010). Several neuromodulatory and neuroimaging studies have highlighted the primary somatosensory cortex (S1) as a key area of the TaMS (Bolognini et al., 2011; Gazzola et al., 2012; Maddaluno et al., 2020; Meyer et al., 2011; Schaefer et al., 2013; Zazio et al., 2019). Interestingly, such embodied simulation processes in the somatosensory domain have been associated with empathy for pain (Lamm et al., 2011) and cognitive empathy in healthy subjects (Bolognini et al., 2013; Bolognini et al., 2014). Moreover, several studies have reported that patients with BPD exhibit abnormal processing of somatosensory stimuli, mainly in terms of nociception (Bohus et al., 2000; Schmahl and Baumgärtner, 2015; Schmahl et al., 2006), but also in tactile sensitivity and affective touch (Cruciani et al. 2023).

The neurophysiological alterations that may underly the impairments in cognitive empathy typical of BPD are far from being understood. To date, neuroimaging studies have shown alterations in mirror-like systems within the sensorimotor areas in BPD; however, the findings are mixed, reporting either hyper- (Sosic-Vasic et al. 2019) or hypo-activation (Mier et al. 2013). Possible alterations in functional connectivity within these systems have not yet been investigated. Although previous studies have described abnormal microstructural and functional brain connectivity in BPD (Orth et al., 2020; Quattrini et al., 2019; Quattrini et al., 2019; Shafiei et al., 2024), evidence of connectivity alterations within the mirror systems in general, or in the TaMS in particular, is lacking. In this context, the combined use of transcranial magnetic stimulation and electroencephalography (TMS-EEG) has proven to be a promising tool for understanding network dynamics, specifically in terms of effective connectivity (Farzan 2024). TMS enables direct activation of a cortical area, whereas EEG traces the spread of cortical activation from the stimulated area to connected areas (Miniussi and Thut, 2010; Momi et al., 2021; Zazio et al., 2021). Interestingly, TMS-EEG has recently been employed to investigate the TaMS in healthy subjects (Pisoni et al., 2018). However, to

the best of our knowledge, it has never been applied to pw-BPD.

In this study, we aimed to investigate empathic abilities and TaMS function in BPD, in terms of behavioral performance and neurophysiological measures of brain connectivity. The study has been preregistered on Open Science Framework (OSF) before data collection to improve scientific reproducibility (OSF). The hypotheses were as follows:

(i) Reduced empathic abilities in the cognitive domain. Based on previous findings (Harari et al. 2010; Martin et al. 2017; Grzegorzewski et al. 2019), we expected lower levels of cognitive empathy in pw-BPD than in healthy controls (HCs). Considering that the literature is less consistent regarding affective empathy, we had no a-priori hypothesis for the comparison between the groups in this dimension.

(ii) Reduced behavioral interference for TaMS activation. When someone is asked to report the side of a touch on their own body and simultaneously observe body parts being touched, as in the visuo-tactile spatial congruency (VTSC) task, S1 activation through the TaMS may impact performance, inducing longer reaction times (RTs; Bolognini et al. 2013, 2014). Specifically, when the observed touches are spatially incongruent with respect to the real touches a negative effect on performance is expected (i.e., interference effect). In pw-BPD, consistent with the hypothesis of reduced cognitive empathy, we expected a reduced interference effect compared to that in HCs, namely a reduced impact of the spatial incongruency of visual touches when directed at human body parts in terms of RTs. Moreover, in HCs, we expected the interference effect in incongruent trials to be greater during visual touches on body parts than in the control condition with visual touches on objects. Finally, in HCs, we hypothesized a negative relationship between cognitive empathy and performance in the VTSC in terms of RT, such that the greater the empathic ability, the greater the interference effect (Bolognini et al. 2013, 2014).

(iii) Altered connectivity pattern during TaMS activation. The TaMS connectivity pattern was indexed by TMS-evoked potentials (TEPs) obtained during the presentation of visual touches on human body parts. Based on previous findings (Bolognini et al. 2014; Maddaluno et al. 2020), we hypothesized that 150 ms would represent the time interval required for S1 to be activated through cross-modal integration within the TaMS network. Therefore, we expected a difference between the pw-BPD and HCs in the TEPs obtained with such time interval and when the visual touch was directed at human body parts but not on objects. We had no a-priori hypothesis on the direction of this effect since hyper- (Sosic-Vasic et al. 2019) and hypo-activation (Mier et al. 2013) of the TaMS have been reported in the literature on BPD, although with different methodologies. Moreover, to rule out the possibility that pw-BPD and HCs show differences in somatosensory reafference (which does not involve the TaMS), the two groups were compared in TEPs obtained when a real touch stimulus was delivered in association with a TMS pulse with a time interval of 20 ms between the two stimuli, which should represent the time interval required for S1 to be activated from peripheral reafference (Cohen et al., 1991).

2. Materials and Methods

2.1 Sample size estimation

To date, no studies on pw-BPD using performance in the VTSC task and TMS-EEG measures as dependent variables have been conducted. Therefore, the present study was a pilot study of these measures. For the sample size estimation, we focused on the comparison between pw-BPD and HCs in empathic levels, considering the works by Harari et al. (2010) and Martin et al. (2017). The sample size was estimated using G*Power (version 3.1.9.7), considering a power of 80% and a threshold for statistical significance of 0.05. The results by Harari et al. (2010) indicated a significant group (pw-BPD and HCs) × empathy (cognitive empathy, affective empathy) interaction ($F(1,40) = 6.38$, $p = 0.016$), with pw-BPD showing a significantly lower cognitive empathy compared to HCs, resulting in a sample size of 12 participants per group. In the study by Martin et al. (2017), pw-BPD showed lower cognitive empathy than HCs ($t(41) = -3.78$, $p < 0.01$), resulting in a sample of 20 participants per group. Taken together, we considered the larger sample size, i.e., 20 pw-BPD and 20 HCs.

2.2 Participants

Twenty-three pw-BPD and 21 HCs were enrolled in the study after providing written informed consent. All participants were right-handed according to the Edinburgh Handedness Inventory (Oldfield 1971), and had no contraindication to TMS (Rossi et al. 2021). All participants received monetary reimbursement for travel expenses. Overall, four participants (three pw-BPD and one HC) did not participate in the TMS-EEG session because their resting motor threshold (rMT) exceeded 82% of the maximal stimulator output (see section 2.4.4). The final sample consisted of 20 pw-BPD (3 men, mean age ± SE: 22.1 ± 0.8 years, range: 18–30 years) and 20 HCs (3 men, mean age ± SE: 23.3 ± 0.9 years, range 20–33 years). Eighteen of the 20 pw-BPD were under pharmacological treatment.

The study was performed in accordance with the ethical standards of the Declaration of Helsinki and was approved by the Ethics Committee of the IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli (Brescia, 65/2020).

2.3 Clinical assessment

Adult patients meeting the inclusion criteria were selected based on a clinical diagnosis of BPD in accordance with the DSM-5 guidelines. The screening process was carried out by the Research Unit of Psychiatry of the IRCCS Fatebenefratelli using a comprehensive psychological evaluation that incorporated the Structured Clinical Interview for DSM-5 Personality Disorders (SCID-5) to ascertain the presence of BPD. Patients were not included in case of comorbidity with schizophrenia and other psychotic disorders, according to DSM-5, and in case of unstable pharmacological therapy.

The severity of the BPD symptoms was assessed using the Zanarini rating scale for BPD (ZAN-BPD (Zanarini et al., 2003)) and the general state-psychopathology with the Symptoms Check-list 90 Revised (SCL-90-R (Derogatis 1994)). Depressive symptoms were evaluated using the Beck Depression Inventory-II (BDI-II (Beck 1988)), impulsiveness with the Barratt Impulsiveness Scale (BIS (Patton et al., 1995)), and alexithymia with the Toronto Alexithymia Scale (TAS-20 (Bagby et al., 1994)). Interpersonal functioning was evaluated using the Interpersonal Problems (IIP) scale (Pilkonis et al., 1996), and attachment style was assessed

using the Attachment Style Questionnaire (Feeney et al., 1994). Finally, the Childhood Trauma Questionnaire (CTQ; (Bernstein and Fink, 1998)) was administered to assess traumatic experiences, and the Inventory of Statements about Self-Injury (ISAS) (Klonsky and Glenn, 2009)) was used to evaluate self-harm.

2.4 Design and procedures

Participants underwent two experimental sessions on separate days, without specific restrictions on the time of day (morning or afternoon). During Session 1, they performed the VTSC task. In Session 2, they underwent the TMS-EEG recording. At the end of session 2, HCs and pw-BPD completed a few self-assessment questionnaires: two questionnaires on empathy levels and one questionnaire on subjective sensations associated with TMS.

2.4.1 Self-report questionnaires

Empathic responses were measured using two self-report questionnaires, assessing cognitive and affective empathy: the Questionnaire of Cognitive and Affective Empathy (QCAE) ((Reniers et al., 2011); Italian version (Di Girolamo et al., 2019)) and the Interpersonal Reactivity Index (IRI) ((Davis 1983); Italian version (Albiero et al., 2006)), both already administered to pw-BPD in previous studies (Harari et al. 2010; Martin et al. 2017; Grzegorzewski et al. 2019). The QCAE comprises 31 statements divided into five subscales (Perspective Taking, Online Simulation, Emotion Contagion, Proximal Responsivity, and Peripheral Responsivity) rated on a 4-point Likert scale from 1 (“strongly agree”) to 4 (“strongly disagree”). The IRI comprises four 7-item subscales (Perspective Taking, Fantasy, Empathic Concern, and Personal Distress) rated on a 5-point Likert scale from 0 (‘‘that does not describe me well”) to 4 (‘‘that describes me very well”).

In the questionnaire on the TMS-related sensations (i.e., pain, hearing noise, cutaneous sensation, heat, coil pressure and muscular movements), developed by our laboratory, participants were asked to report the intensity of the subjective sensation and the associated discomfort, on a Likert scale from 0 (“nothing”) to 4 (“very intense”).

2.4.2 VTSC task

The VTSC task was adapted from Bolognini et al. (2014), which, in turn, referred to Banissy and Ward (2007). Participants were comfortably seated 75 cm from a computer monitor (LCD, resolution 1280 × 800, refresh rate 60 Hz; head position ensured using a chinrest), on which they were presented with a left and a right hand from an egocentric perspective (stimuli eccentricity: 8° visual angle; illuminance: 1.3 lux - Hands block). In each trial (**Figure 1A**), another hand in an allocentric perspective appeared on the top of the screen and moved towards either the left or the right hand in 100 ms-frames; the final frame (1000 ms duration; illuminance: 2.2 lux) showed the allocentric hand touching one of the egocentric hands (visual touch). Ten milliseconds after the beginning of the visual touch, a real tactile stimulus (real touch) was delivered either to the participants' left or right hand, administered through miniature solenoid tappers (visuo-tactile trials). Visual and real touches were spatially congruent or incongruent. In unimodal trials, only the visual (visual only) or real touch (tactile only) was presented. Participants were asked to fixate on a red asterisk in the center of the screen and report the side of the real touch by pressing a button on a computer keyboard. The performance was evaluated in terms of accuracy and RTs. In the catch-no-touch trials, the

color of the fixation cross changed to green, and no touches (neither visual nor real) were presented. In these trials, the participants were asked to press both response buttons. Catch-no-touch trials ensured that the participants maintained fixation on the center of the screen. In the control block, the two hands from the egocentric perspective were replaced with two objects (i.e., two leaves - Leaves block; illuminance range: 2.2-3.2 lux). The block order was counterbalanced across participants.

At the end of each block, participants were asked to report their sensations on a brief questionnaire using a visual analog scale (VAS). The questionnaire comprised the following items: (1) “When I was shown with a *hand/leaf* being touched, I had the feeling of being touched on my own hand (2) “Looking at the *hand/leaf* being touched made it difficult to localize the tactile stimulus on my own hand”.

The experiment was run in E-Prime software (E-Prime 2.0, Psychology Software Tool, Inc., Sharpsburg, PA, USA). The timing of stimulus delivery was verified using a photodiode (for visual stimuli) and a pressure sensor (for tactile stimuli).

2.4.3 TMS-EEG

EEG signals were recorded at a sampling rate of 9600 Hz from 74 TMS-compatible passive Ag/AgCl electrodes (EasyCap, BrainProducts GmbH, Munich, Germany) using a TMS-compatible system (g.HIamp, g.tec Medical Engineering GmbH, Schiedlberg, Austria) in an electromagnetically shielded room. No filters were applied during the recording and the skin-electrode impedance was kept below 5 kΩ.

The TMS pulses were delivered using a Magstim Rapid2 stimulator (Magstim Company, Whitland, UK) with a 70 mm figure-of-eight coil (Alpha B.I.), which produced a biphasic waveform. The orientation of the coil was approximately 45° from the midline so that the direction of the current flow in the right S1 during the second phase of the pulse waveform was posterior-to-anterior (Sommer et al. 2006; Siebner et al. 2022). The charge delay was set at 350 ms and the coil position was monitored using the Softaxic 3.4.0 neuronavigation system (EMS, Bologna, Italy). To attenuate the contamination of the TEPs with sensory artifacts, the participants wore noise-canceling earphones playing white noise, and a thin layer of foam was applied under the coil.

First, the motor hotspot for the left first dorsal interosseous (FDI) muscle was localized at the scalp location eliciting the highest and most reliable motor-evoked potentials (MEPs) at the same TMS intensity. The rMT was then estimated using the maximum-likelihood threshold-hunting algorithm (Awiszus 2003, 2011), a variant of the best parameter estimation by sequential testing (best PEST) procedure (Pentland 1980). MEPs during rMT estimation were not recorded. Once the individual rMT was determined, the location of the right S1 was identified by moving the TMS coil 2 cm lateral and 0.5 cm posterior to the hotspot for FDI (Holmes and Tamè, 2019). The TMS intensity was set at 110% of the rMT.

During the TMS-EEG session, participants were presented with real touches delivered to the left hand using a solenoid tapper, and with visual touches presented in the center of a computer screen (equal to the VTSC task, placed 75 cm from the participants; head position was ensured by using a chinrest). Visual touch consisted of touching the left hand (illuminance range: 0.6-0.9 lux) or a leaf (illuminance range: 1.2-1.5 lux). TMS and no-TMS trials were

included. In the TMS trials, a TMS pulse was delivered over the participant's right S1 after a visual or real touch stimulus. The inter-stimulus interval (ISI) between the visual/real touch stimulus and TMS was either 20 or 150 ms (**Figure 1B)**. The no-TMS trials were identical to the TMS trials, except that TMS was not delivered after the visual/real touch stimuli. Based on pilot data (see preregistration on OSF), these trials were used to extract event-related potentials (ERPs) for visual and real touch stimuli. For each of the nine conditions (TMS trials: 3 × 2, trial type × ISI; no-TMS trials: 3 trial types), 77 trials were presented, divided into seven blocks, and trial order was randomized. To maintain the participants' attention to the visual stimuli, 28 catch trials that required participants' responses were included. TMS was not delivered during the catch trials. The number of trials was determined to obtain a good signal-to-noise ratio in TEPs based on previous TMS-EEG studies (e.g., Bortoletto et al., 2021) and on the pilot experiment, while keeping the total duration of the experiment as short as possible, considering the involvement of a clinical population.

The experiment was run in E-Prime software (E-Prime 2.0, Psychology Software Tool, Inc.). The timing of stimulus delivery was verified using a photodiode (for visual stimuli) and a pressure sensor (for tactile stimuli).

2.4.4 Exclusion criteria

Participants were excluded from the sample in the following cases: (i) they did not complete all blocks of the VTSC session; (ii) performance at catch trials ('catch-no-touch' trials in the VTSC and 'catch' trials in the TMS-EEG session) was below 50%; (iii) in the VTSC session, RTs or number of errors in at least one condition deviated of more than 2.5 SD from the sample mean; (iv) in the TMS-EEG session, 110% of rMT exceeded 90% of the maximal stimulator output; (v) in the TMS-EEG session, the final TEPs obtained for each trial type comprised less than 54 trials (i.e., 70% of the planned 77 trials) (**Figure 2A-B**).

2.5 Analysis

2.5.1 Self-report questionnaires

For the QCAE, the measure for cognitive empathy was obtained using the sum of scores of the Perspective Taking and Online Simulation subscales, and for affective empathy using the sum of scores of the Emotion Contagion, Proximal Responsivity, and Peripheral Responsivity subscales. For the IRI, the measure for cognitive empathy was obtained using the sum of scores of the Perspective Taking and Fantasy subscale, and for affective empathy using the sum of scores of the Empathic Concern and Personal Distress subscales. Normative data for the Italian population (Maddaluno et al., 2022) were applied to the raw values for exploratory analyses.

2.5.2 Behavioral data

Individual RTs were log10-transformed, and trials exceeding ± 2 SD of the individual mean were discarded. The average value for each trial type was considered for statistical analyses. The accuracy was measured in terms of the number of errors.

2.5.3 TMS-EEG data

One pw-BPD was excluded from the analyses because she did not complete all TMS-EEG blocks owing to discomfort during TMS delivery and the minimum number of trials was not reached (see exclusion criteria). Thus, a sample of 20 HCs and 19 pw-BPD was used for the ERP and TEP analyses. TMS-EEG data processing was performed in MATLAB R2020b (The Mathworks, Natick, MA, USA) with custom scripts using EEGLAB v.2020.0 (Delorme and Makeig, 2004) and FieldTrip functions (Oostenveld et al., 2011), following the same steps applied by our research group in previous studies (Guidali et al., 2023; Zazio et al., 2022). Unless otherwise specified, default parameters for the EEGLAB and FieldTrip functions were used.

For each participant, the first preprocessing step included all the trial types. This procedure ensured that the same preprocessing steps were applied to all conditions, thereby minimizing the risk of differences between conditions arising from dissimilarities between the preprocessing steps. Continuous TMS-EEG data were interpolated for 3 ms around the trigger to eliminate TMS pulse-induced artifacts, high-pass filtered at 1 Hz (FIR sync filter, EEGLAB function 'pop_eegfiltnew,' order 31682), downsampled to 4800 Hz and epoched from -750 ms before to 750 ms after the stimulus. Subsequently, the source-estimate-utilizing noise-discarding (SOUND) algorithm was applied to discard noise measurement (spherical 3-layer model, regularization parameter: λ=.01 (Mutanen et al. 2018) followed by a first round of automatic artifact rejection on the epochs (EEGLAB function 'pop_jointprob,' threshold for rejection: 5 SD). No channels were rejected. Then, ocular artifact correction was performed using Independent Component Analysis (ICA; EEGLAB function 'pop_runica,' infomax algorithm, 73 channels included, 73 ICA components calculated): the horizontal and vertical eye movement components were visually inspected and discarded based on topographical maps (vertical movements: strong positive peak on frontal electrodes, symmetrically distributed with decreasing amplitude toward posterior regions; horizontal movements: opposite polarity in lateral frontal-temporal electrodes), power spectrum (characterized by a peak of activity at low frequencies), and temporal distribution over trials (isolated events at random time points in TMS pulse-locked epochs). The signal-space projection and source-informed reconstruction (SSP-SIR, (Mutanen et al. 2016) algorithm was then applied to remove TMS-evoked muscle artifacts in the first 50 ms after the TMS pulse; the principal components were visually inspected and discarded if they represented a high-frequency (i.e., > 100 Hz) signal time-synchronized with the TMS pulse. Finally, the data were filtered with a 70 Hz low-pass filter (IIR Butterworth filter, order 4, EEGLAB function 'pop_basicfilter') and re-referenced to the common average reference. The ICA and SSP-SIR steps were performed by two independent researchers. Then, epochs were redefined around the trigger in the range of -200 ms to 400 ms, the baseline was corrected to -200 ms to -2 ms, and a second manual artifact rejection was performed to discard residual artifactual trials (i.e., epochs visualized in the time domain in which signal amplitude or oscillatory activity deviated significantly from other trials). At this point, the data were divided according to trial type.

The same pipeline, except for interpolation in the time interval of the TMS pulse and SSP-SIR, was run for non-TMS trials to obtain the ERPs generated by the presentation of the visual stimuli (baseline), as well as ERPs generated by the visual touch stimuli (i.e., real touches and visual touches on the hand or on the leaf).

After preprocessing, the data were converted into FieldTrip structures for visualization and statistical analysis.

In the exploratory analysis of the TEP peaks, we focused on the early components within 100

ms to avoid confounding factors related to TMS sensory processing (Herring et al., 2019; Niessen et al., 2021; Nikouline et al., 1999). The peak amplitudes and latencies were extracted from electrode CP4, which showed the highest signal of all components in the mean of all conditions, by averaging over 10 ms around the peak.

2.5.4 Statistical analysis

If not otherwise specified, the statistical analyses followed what was planned in the preregistration.

I. *Self-report questionnaires:* For each questionnaire on empathic levels (i.e., QCAE and IRI), we ran a 2 × 2 repeated-measures analysis of variance (rm-ANOVA) with within-factor type (cognitive empathy, affective empathy) and between-factor group (HCs, pw-BPD). Exploratory analyses tested for group differences in TMS-related sensations by means of non-parametric U Mann-Whitney test for independent samples.

   Exploratory descriptive analyses included the application of IRI score correction based on normative Italian data (Maddaluno et al. 2022), to obtain equivalent scores for each participant.

II. *VTSC task:* As preliminary analyses, independent t-tests compared HCs and pw-BPD in terms of accuracy in visual-only trials and RT in tactile-only trials to rule out the presence of generic group differences. Thus, the possible differences between the groups may be attributed to the activity of the TaMS. Then, on the visuo-tactile trials, we ran a 2 × 2 × 2 rm-ANOVA on RTs with within factors stimulus (hands, leaves) and congruency (congruent, incongruent), and between factor group (HCs, pw-BPD). Although the main hypotheses were on RTs, we also planned exploratory analyses on accuracy (i.e., number of errors) for which we applied non-parametric tests owing to ceiling effects: U Mann-Whitney for the preliminary analysis, and the 2 × 2 × 2 Aligned Rank Transform (ART)-ANOVA with within factors stimulus (hands, leaves) and congruency (congruent, incongruent), and between factor group (HCs, pw-BPD).

   Regarding the expected effects in HCs, a correlation was first used to test the relationship between cognitive empathy scores and the interference effect at the VTSC, defined as the difference in RT between incongruent and congruent trials in the Hands block. Second, a one-tailed t-test for dependent samples was used to compare the interference effect between the Hands and Leaves blocks.

   Exploratory analyses of RTs included the comparison between visuo-tactile congruent, visuo-tactile incongruent, and unimodal tactile-only trials by means of a 3 × 2 rm-ANOVA with within-factor trial type (congruent, incongruent, tactile-only) and between factor group to reveal whether visual touch shortened or lengthened the RT in unimodal tactile-only trials. This analysis was performed separately for the Hands and Leaves blocks. Finally, we subtracted visuo-tactile trials (i.e., congruent and incongruent trials) from tactile-only trials, to obtain a normalized RT score (ΔRTnorm) based on individual RT. The ΔRTnorm was added to the 2 x 2 x 2 stimulus x congruency x group rm-ANOVA described above.

   Exploratory analyses of the responses to the questionnaire on the sensations induced

by the VTSC were performed separately for each question using ART-ANOVA.

III. *TMS-EEG:* The preregistration included two analyses on TEPs: First, considering TEPs obtained from visual touch (touch-hand and touch-leaf) trials with ISI-150 in HCs and pw-BPD, and testing for an interaction effect in a 2 × 2 mixed between-within-subjects design. TEPs from touch-leaf trials were subtracted from TEPs from touch-hand trials and then compared between HCs and pw-BPD using a two-tailed non-parametric cluster-based permutation test for independent samples over all channels and time points from 4 to 350 ms after the TMS pulse (Maris and Oostenveld, 2007). Second, the same statistics were applied to compare TEPs obtained from real-touch trials using ISI-20 in HCs and pw-BPD.

ERP analyses were exploratory. ERPs were calculated for no-TMS trials, i.e., those generated by the presentation of the hand or the leaf before the touch occurred (baselineERPs), as well as those generated by the presentation of the visual or real touch (touchERPs).

Exploratory analyses of TEPs with ISI-20 and ERPs from visual-touch trials followed the same approach, where applicable. We tested the main effects of stimulus and group, and the stimulus × group interaction by means of two-tailed non-parametric cluster-based permutation tests. Specifically, the main effect of stimulus was tested by concatenating data from HCs and pw-BPD, and then performing a t-test for dependent samples, while the main effect of group was tested by averaging signals from Hand and Leaf trials, and performing a t-test for independent samples. As in the preregistered analysis of TEPs with ISI-150, the interaction was tested by subtracting signals in Leaf trials from signals in Hand trials. Cluster-based analyses of TEPs were performed from 4 to 350 ms after the TMS pulse, whereas cluster-based analyses of ERPs started from 1 ms after stimulus onset. All analyses were performed over all channels.

Finally, an exploratory analysis of the TEP-ERP difference was performed on the amplitudes and latencies of the peaks of the main components, which were entered into a 2 × 2 × 2 stimulus × ISI × group rm-ANOVA. In this case, the threshold for significance was corrected for the two peaks (0.05/2=0.025). HCs and pw-BPD were also compared in terms of rMT using an independent t-test.

The threshold for statistical significance was set at $p < 0.05$. Rm-ANOVAs and t-test comparisons were performed in Jamovi (The jamovi project 2.3.21, 2021; R Core Team, 2020), while the ART-ANOVA was performed in R using the ARTool package (Elkin et al., 2011). Statistics on neurophysiological measures (i.e., TEPs and ERPs) were performed in MATLAB R2020b (The Mathworks) using FieldTrip functions (Oostenveld et al. 2011). Reported *p* values were corrected for multiple comparisons (Tukey correction for data from questionnaires, the VTSC task, and TEP peaks, and cluster correction for the analysis of TEPs and ERPs over all channels and time points). In cluster-based analysis, the reported time intervals for significant clusters are intended as approximate latencies (Sassenhagen and Draschkow, 2019).

3. Results

If not otherwise reported, data were normally distributed according to the Shapiro-Wilk test, and mean ± SE are reported in parentheses.

3.1 Clinical evaluation

Average scores at the clinical assessment of pw-BPD are reported in **Table1**. From a clinical perspective, pw-BPD exhibited moderate levels of BPD symptoms, impulsiveness, and depression. More than 80% of the participants reported self-harm behaviors. BPD was the primary diagnosis for all patients, with 6 out of 20 pw-BPD also presenting comorbidities with one or two other psychiatric disorders, including: avoidant personality disorder, obsessive-compulsive disorder, eating disorder, post-traumatic stress disorder, panic attack disorder, generalized anxiety disorder. In terms of substance use, 43.8% of pw-BPD reported current alcohol abuse, while 26.7% reported a history of alcohol abuse. As for drug use, 31.3% of pw-BPD reported both current and past drug abuse.

	N	Mean	±	SE
Zanarini rating scale for Borderline Personality Disorder (ZAN-BPD)	13	10.54	±	3.6
Baratt Impulsiveness Scale (BIS-11)	14	70.29	±	11.07
Beck Depression Inventory (BDI_II)	14	29.21	±	13.99
Toronto Alexithymia Scale (TAS)	14	60.79	±	13.05
Symptom Checklist-90-R (SCL90)	13	168.92	±	78.73
Inventory of Interpersonal Problems (IIP)	14	2.08	±	0.65
Childhood Trauma Questionnaire (CTQ)	15	51.27	±	13.06
Attachment Style Questionnaire (ASQ)	14			
Confidence		*23.71*	±	*6.52*
Discomfort with Closeness		*42.5*	±	*4.78*
Relationships as secondary		*18.36*	±	*9.68*
Need for Approval		*29.86*	±	*7.59*
Preoccupation with Relationships		*36.93*	±	*6.03*
Inventory of statements about self-injury (ISAS)	19			
Presence of self-injury (%)		*84.21%*		

Table 1. Test scores at the clinical assessment of patient with borderline personality disorder. N indicates the number of participants who completed the questionnaires.

3.2 Self-report questionnaires

Overall, the questionnaire data indicated impaired cognitive empathy in pw-BPD (**Figure 3**). The results on the QCAE highlighted a significant empathy x group interaction ($F(1,38) = 12.9$, $p = 0.001$, $\eta^2_p = 0.25$), with post-hoc analyses revealing lower cognitive empathy in pw-BPD compared to HCs ($t = 2.94$, $p = 0.028$; **Table 1**). We also observed a main effect of empathy ($F(1,38) = 316.34$, $p < 0.001$, $\eta^2_p = 0.89$), showing higher values for cognitive empathy (57.7 ± 1.6) compared to affective empathy (36.9 ± 0.85), and a significant main effect of group ($F(1,38) = 4.20$, $p = 0.047$, $\eta^2_p = 0.10$), with HCs (49.5 ± 1.48) showing overall greater empathic levels compared to pw-BPD (45.2 ± 1.48). For the IRI, the empathy x group interaction showed a trend towards statistical significance ($F(1,38) = 3.76$, $p = 0.06$, $\eta^2_p = 0.09$), with pw-BPD

showing lower scores in cognitive empathy compared to HCs (**Table 1**). As for the QCAE, we observed a significant main effect of empathy (F(1,38) = 4.341, p = 0.0.044, η^2_p = 0.1), and post-hoc comparisons revealed higher levels of cognitive empathy (35.97 ± 1.44) compared to affective empathy (33.1 ± 1.17). The main effect of Group was not significant (F(1,38) = 1.76, p = 0.192, η^2_p = 0.04). Based on the IRI normative values (Maddaluno et al. 2022), seven of the 20 pw-BPD were found to be below the threshold for the normal range (i.e., equivalent score of 0), indicative of a defective score, and three of the 20 pw-BPD showed a borderline score for the normal range (i.e., equivalent score of 1) in at least one of the subscales. Among HCs, only one of the 20 reported an equivalent score of 1.

Results from the TMS-related sensation showed no differences between groups (p > 0.1; details are reported in Supplementary **Table S1**).

3.3 VTSC

Taken together, the VTSC results showed that pw-BPD performed worse than HCs in terms of accuracy (i.e., a higher number of errors) when hand touches were presented, while the RTs were affected by spatial congruency between the visual and tactile stimuli in both groups.

Regarding accuracy, preliminary analyses showed that performance in catch-no-touch trials was above 50% in all cases, indicating that participants were attending to the visual stimuli. Moreover, HCs and pw-BPD did not differ in the number of errors in visual-only trials (Hands: U = 180, p = 0.482; Leaves: U = 152, p = 0.111), in which they were asked not to provide a response. On visuo-tactile trials, two pw-BPD and one HC were excluded as their data exceeded the ± 2.5 SD from the mean, leaving 18 pw-BPD and 19 HCs for the analyses on VTSC accuracy. ART-ANOVA indicate that pw-BPD performed worse than HCs, independently of the content of the visual stimulus or its spatial congruency with the tactile stimulus. The results showed a significant main effect of group (F(1,35) = 27.3, p < 0.001), with pw-BPD making more errors than HCs (pw-BPD: 1.85 ± 0.31; HCs: 0.32 ± 0.06), and a main effect of congruency (F(1,105) = 36.2, p<0.001), with more errors in incongruent trials (1.45 ± 0.25) compared to congruent trials (0.68 ± 0.22). The main effect of stimulus was not significant (F(1,105) = 0.2, p = 0.7), as well as the interactions (p > 0.079).

Regarding RTs, one HC exceeded ± 2.5 SD from the mean and was therefore excluded, leaving 19 HCs and 20 pw-BPD for the VTSC analyses. The preliminary analysis showed no significant differences in RT in tactile-only trials between HCs and pw-BPD, neither in the Hand (t = -1.52, p = 0.138) nor in the Leaves block (t = -1.12, p = 0.268), indicating that the two groups did not show non-specific differences in RTs. Importantly, the rm-ANOVA on visuo-tactile trials revealed a significant main effect of congruency ($F(1,37)$ = 59.35, p < 0.001, η^2_p = 0.62), with slower RTs in incongruent trials (mean ± SE: 2.56 ± 0.014) compared to congruent trials (mean ± SE: 2.54 ± 0.014). No other main effects (stimulus: $F(1,37)$ = 0.08, p = 0.772, η^2_p = 0.002; group: $F(1,37)$ = 1.19, p = 0.283, η^2_p = 0.03) or interactions (stimulus x group: $F(1,37)$ = 1.54, p = 0.223, η^2_p = 0.04; congruency x stimulus: $F(1,37)$ = 0.90, p = 0.348, η^2_p = 0.02; congruency x stimulus x group: $F(1,37)$ = 0.006, p = 0.940, η^2_p = 0.00) were significant. The mean values of the raw RTs and error numbers are listed in **Table 2**.

Exploratory analyses did not reveal additional group differences. We observed an overall advantage in terms of RTs in visual-touch trials compared to unimodal tactile-only trials, and a higher subjective sensation of being touched during the Hand block than during the Leaves

block. Specifically, in the rm-ANOVA on RTs including congruent, incongruent and tactile-only trials, we observed a main effect of trial type for the Hands ($F(2,74) = 84.74$, $p < 0.001$, $\eta^2_p = 0.7$) and Leaves blocks ($F(2,74) = 43.94$, $p < 0.001$, $\eta^2_p = 0.54$). Post-hoc comparisons showed longer RTs for unimodal tactile-only trials compared to incongruent and congruent visuo-tactile trials, and RTs in incongruent trials were longer than those in congruent trials ($p < 0.001$ in all comparisons). The main effect of group was not significant in the Hands ($F(1,37) = 2.21$, $p = 0.145$, $\eta^2_p = 0.06$) and the Leaves blocks ($F(1,37) = 0.99$, $p = 0.327$, $\eta^2_p = 0.03$), neither was the trial type × group interaction (Hands: $F(2,74) = 0.42$, $p = 0.658$, $\eta^2_p = 0.01$; Leaves $F(2,74) = 1.3$, $p = 0.278$, $\eta^2_p = 0.034$). Finally, results on RTnorm were comparable to the preregistered analyses, namely showing a main effect of congruency ($F(1,37) = 61.7$, $p < 0.001$) in the absence of other significant effects ($p > 0.11$).

The analyses on the sensations induced by the VTSC highlighted a significant main effect of stimulus in the sensations described in Item-1 (*"When I was shown with a hand/leaf being touched, I had the feeling of being touched on my own hand";* $F(1,37)$ $p < 0.001$), showing higher scores for the Hands block than for the Leaves block for both pw-BPD and HCs. The main effect of group ($F(1,37)$, $p=0.068$) and the group by stimulus interaction ($F(1,37)$, $p=0.41$) did not reach the significance level. With respect to Item-2 (*"Looking at the hand/leaf being touched made it difficult to localize the tactile stimulus on my own hand"*), no significant effects emerged ($p > 0.254$).

		HC N(F)=20(17)			pw-BPD N(F)=20(17)		
		Mean	±	SE	Mean	±	SE
Age in years		23.3	±	0.9	22.1	±	0.8
Education in years		14.6	±	0.6	12.1	±	0.7
QCAE							
	Perspective Taking	32.35	±	0.96	28.79	±	1.75
	Online Simulation	29.5	±	0.78	24.37	±	1.71
	Emotion Contagion	11.7	±	0.56	12.42	±	0.51
	Proximal Responsivity	12.7	±	0.39	12.05	±	0.66
	Peripheral Responsivity	12.55	±	0.3	12.11	±	0.74
	Cognitive Empathy	61.95	±	1.45	53.16	±	2.66
	Affective Empathy	36.95	±	0.99	36.58	±	1.46
IRI							
	Perspective Taking	19.3	±	0.65	16.6	±	1.59
	Fantasy	19.5	±	0.94	16.55	±	1.57
	Empathic Concern	20.7	±	0.67	17.35	±	1.3
	Personal Distress	12.55	±	0.76	15.6	±	1.09
	Cognitive Empathy	38.8	±	1.26	33.15	±	2.6
	Affective Empathy	33.25	±	1.12	32.95	±	2.06
VTSC task - *number of errors*							
Visual touch congruent (Hands)		0.11	±	0.07	0.94	±	0.29
Visual touch incongruent (Hands)		0.53	±	0.14	2.50	±	0.64
Visual touch congruent (Leaves)		0.11	±	0.07	1.61	±	0.81
Visual touch incongruent (Leaves)		0.53	±	0.18	2.33	±	0.62

VTSC task - *RTs*						
Visual touch congruent (Hands)	344.89	±	13.82	384.97	±	22.12
Visual touch incongruent (Hands)	355.68	±	15.64	378.20	±	22.97
Visual touch congruent (Leaves)	364.39	±	13.20	415.13	±	21.38
Visual touch incongruent (Leaves)	374.02	±	15.90	404.19	±	23.51
Tactile-only (Hands)	405.79	±	15.94	452.13	±	21.28
Tactile-only (Leaves)	412.75	±	16.82	450.93	±	23.26

Table 2. Descriptive data for patients with borderline personality disorder (pw-BPD) and healthy controls (HCs). Demographics, average scores obtained at the different subscales of the Questionnaire of Cognitive and Affective Empathy (QCAE) and Interpersonal Reactivity Index (IRI) questionnaires, average raw reaction times (RTs) and number of errors recorded during the different trial types of the visuo-tactile spatial congruency (VTSC) task.

3.4 Exploratory ERPs

Exploratory analyses on ERPs followed a cluster-based approach over all channels and time points. For baselineERPs – elicited by the presentation of the hand or leaf before the visual touch occurred – and touchERPs, generated by the touch frame on the hand or leaf, the statistical design resembled a 2x2 Stimulus by Group ANOVA. In contrast, real-touchERPs, generated by tactile stimulation were compared between HCs and pw-BD using an independent samples t-test.

BaselineERPs were affected by the stimulus, in the absence of differences between HCs and pw-BPD. We observed three significant clusters: two positive (p = 0.03, from 70 ms to 110 ms over the frontal and lateral right electrodes; p = 0.002 from 100 ms to 200 ms over the frontocentral electrodes) and one negative (p = 0.002, from 70 ms over the posterior central electrodes). The N170, a component typically generated in response to images of faces and body parts (Kovács et al. 2006), was present in baselineERPs (Hand) but not in baselineERPs (Leaf) (**Figure 4**). No significant clusters were present either for the main effect of group (p = 1) or stimulus × group interaction (p = 1).

For touchERPs, the results suggested a different pattern for pw-BPD and HCs, depending on the visual stimulus. The stimulus × group interaction showed a trend towards significance in one positive cluster (p = 0.066). Exploratory direct comparisons between touchERP(Hand) and touchERP(Leaf) within each group revealed two significant clusters in pw-BPD: one positive (p = 0.014) from 215 to 280 ms over the frontal right electrodes, and one negative (p = 0.014) from 185 to 290 ms over the posterior left electrodes, showing reduced ERPs components during human-directed touch compared to object-directed touch. No significant clusters emerged in the HCs (p > 0.304). Finally, no significant clusters emerged for the main effects of stimulus (p > 0.102) or group (p > 0.436).

Finally, real-touchERPs did not differ between HCs and pw-BPD, as no significant clusters emerged (p > 0.753).

3.5 TEPs

Preliminary analyses showed that during TMS-EEG, the accuracy in catch trials was always above 50%, indicating that all participants attended the visual stimuli. Moreover, the rMT did not differ between HCs (mean ± SE: 61.1 ± 2.1) and pw-BPD (mean ± SE: 60.5 ± 2.5; p=0.856).

Preregistered cluster-based analysis showed that TEPs were modulated by the content of the visual stimulus when TMS was delivered 150 ms after touch onset but did not show differences between groups, indicating specific TaMS alterations in pw-BPD. Indeed, in visual-touch trials with ISI-150, we observed two significant clusters for the main effect of stimulus: one positive over posterior electrodes (p = 0.002) and one negative over fronto-central electrodes (p = 0.002), both from approximately 230 to 350 ms, resulting in reduced TEP components during touches on the leaf compared with touches on the hand (**Figure 5A**). No clusters emerged for the main effect of group (p > 0.142) or stimulus × group interaction (p > 0.548). Furthermore, no significant effects were found in exploratory analyses of TEPs with ISI-20 in visual touch trials, neither for the main effect of stimulus (p > 0.19),the main effect of group (p > 0.18), nor for the stimulus × group interaction (p > 0.59).

Regarding TEPs recorded after real touches, exploratory cluster-based analyses indicated differences between pw-BPD and HCs when TMS was delivered 150 ms after the real touch. While no significant clusters emerged in the preregistered analysis on ISI-20 trials (p > 0.57), exploratory analyses on ISI-150 trials revealed two significant clusters (one positive, between 130 and 240 ms over left fronto-central electrodes, p = 0.032; one negative, between 100 and 240 ms over right posterior central electrodes, p = 0.034), revealing reduced TEP amplitudes in pw-BPD compared to HCs (**Figure 5B**).

3.6 Exploratory: ΔTEP-ERP peaks

Analyses of ΔTEPs-ERPs indicated a different connectivity pattern between HCs and pw-BPD, which was independent from the ISI and the visual stimulus (**Figure 6**; see **Supplementary Figure S1** for an example of the subtraction process in visual touch trials in HCs). Peak amplitude and latency were extracted from two TEP components in the ΔTEPs-ERPs, namely N15 and P60. A significant main effect of group emerged for P60 ($F(1,37) = 6.92$, p = 0.012), with pw-BPD showing lower amplitudes (mean ± SE: 3.19 ± 0.88 μV) than HCs (mean ± SE: 6.43 ± 0.86 μV). No other significant main effects or interactions were observed for the other peaks in terms of either amplitude or latency (summary results are provided in Supplementary **Table S2**).

4. Discussion

In the present preregistered study, in pw-BPD and HCs we investigated and compared the empathic abilities, behavioral performance in a task involving TaMS activity, and neurophysiological measures obtained from TMS-EEG recordings. The main findings showed that pw-BPD had significantly lower cognitive empathy, performed worse in terms of accuracy in the VTSC task involving TaMS activity, and displayed a different connectivity pattern in the TMS-EEG data, although both behavioral and neurophysiological results appeared not to be

specific for TaMS.

Regarding empathic abilities, our findings suggest that pw-BPD have difficulties understanding and imagining others' perspectives rather than feeling others' sensations and experiencing their emotions. Specifically, the QCAE results showed significantly lower levels in the cognitive domain in pw-BPD than in HCs; however, there was no difference in the affective domain, which is consistent with existing findings (Grzegorzewski et al. 2019). Although the results for the IRI on cognitive empathy did not reach statistical significance, similar to previous reports (Harari et al. 2010; Martin et al. 2017), they showed a trend towards the same direction. Furthermore, in addition to previous studies, we used normative values for the IRI scores (Maddaluno et al. 2022), showing that they were below or at the lower boundary of the normal range in half of the pw-BPD. This finding highlights the significance of empathic impairment as a hallmark of BPD, although variability of empathy deficits within this population must be acknowledged. Considering that the QCAE has been suggested to overcome some intrinsic limitations of the IRI, both from psychometric (Chrysikou and Thompson 2016) and theoretical (Michaels et al. 2014) perspectives, its results may offer a more refined insight into empathic abilities in pw-BPD. Nevertheless, future studies could further explore the two measures to better clarify the nuances of empathic abilities in pw-BPD.

We employed the VTSC task to test if such impairments in cognitive empathy in BPD reflect alterations in the activity of mirror-like mechanisms in the somatosensory domain (Keysers et al. 2010). Indeed, the VTSC task is an established behavioral paradigm to study the TaMS, as seeing a touch on human body parts is expected to activate the TaMS, and the spatial incongruency between the seen and felt touches should interfere with the ability to report the side of the real touch (Banissy and Ward, 2007; Bolognini et al., 2013, 2014). Several quality checks supported the VTSC task functioning as in previous studies. First, both RTs and accuracy performance were affected by the spatial congruency of the touching hand in relation to the real touch, indicating that the location of the visual stimulus was relevant for performing the task. Exploratory analyses on RTs also revealed that visual touch trials were faster than in unimodal tactile-only trials, showing typical crossmodal facilitation (Macaluso and Maravita, 2010). Moreover, the 2-item questionnaire on the sensations induced by the VTSC task showed a difference between the Hands and Leaves blocks, indicating that both HCs and pw-BPD had a more intense feeling of being touched on their own hands while viewing a human hand being touched (i.e., Hand block) than during the view of an object being touched (i.e., Leaves block), with no differences observed in terms of localization difficulties.

Given the lower levels of cognitive empathy in pw-BPD, we predicted a reduced interference effect in this group compared to HCs on the VTSC task in terms of RTs. Our results did not show behavioral evidence of TaMS alteration in pw-BPD, neither on RTs nor on accuracy. Nevertheless, we observed a group difference in accuracy, independent of spatial congruency and stimulus type, with pw-BPD making more errors than HCs while exhibiting similar RTs. These findings suggest that pw-BPD may have an alteration within the somatosensory system's ability to process visuo-tactile stimuli, although this was not specific for stimuli activating the TaMS. The nature of such impairment needs to be further addressed by future research, as the possibility of more unspecific tactile deficits cannot be entirely excluded in the present work. In addition, considering that performance exhibited ceiling effects for HCs in accuracy, in future studies the VTSC task could be refined to enhance sensitivity, hence increasing the changes of cross-modal, visual, effects on tactile processing.

It should be considered that the link between the VTSC and emphatic abilities need to be further understood in future research. Indeed, HCs did not show a significant difference in RTs between human- and object-directed visual touches, nor a significant relationship between cognitive empathy and VTSC performance. Such effects have been previously reported in healthy participants (Bolognini et al. 2013, 2014); however, they were observed only after experimental modulation of S1 activity by means of TMS or transcranial electrical stimulation, a crucial difference from the present paradigm. Therefore, our results on HCs should not be interpreted as in contrast to previous studies.

Regarding the neural correlates of mirror mechanisms in BPD, the existing literature presents a variety of experimental paradigms, and most of the evidence in this context comes from functional magnetic resonance imaging studies during the observation of visual stimuli with emotional content, showing an increased or decreased pattern of activation in brain areas belonging to the mirror neuron system (Mier et al. 2013; Sosic-Vasic et al. 2019). In contrast, results from studies employing emotionally neutral stimuli, as in the present one, seem more subtle, with pw-BPD showing a trend for a different pattern of mu-desynchronization compared to HCs only at specific time points in an action observation task (Martin et al. 2017). Here, the experimental design of TMS-EEG recording allowed us to investigate the integrity of the somatosensory network beyond the mirroring activation of the TaMS by touch observation, extending to the processing and connectivity patterns associated with tactile perception.

TMS-EEG has recently emerged as a promising technique for identifying biomarkers in psychiatry (Farzan 2024), and to the best of our knowledge, the current study is the first to present TEP data from pw-BPD. Employing TMS during a task is known to enable the investigation of network-specific activity which is dependent on its functional status (Barchiesi et al., 2022; Jacquet and Avenanti, 2015; Silvanto et al., 2007), while the simultaneous recording of EEG provides information on the spread of neural activation to brain areas effectively connected to the stimulated one (Bortoletto et al., 2015; Massimini et al., 2005; Zazio et al., 2021). Crucially, combining the two techniques in TMS-EEG recordings when participants perform a task allows for the investigation of brain connectivity in task-specific networks (Morishima et al. 2009; Bortoletto et al. 2021; Zazio et al. 2022). In pw-BPD and HCs and under all conditions, we successfully recorded clear TEP components from S1 stimulation, namely the N15, P60, N100, P200, and P300, with topographical patterns similar to those described previously for HCs (Pisoni et al. 2018). When considering HCs and pw-BPD together, a difference between the observation of human- and object-directed visual touches occurred at late TEP latencies, namely from 200 ms from the TMS pulse onset. This finding suggests that TaMS activity involves S1 connections with distant areas (Bortoletto et al. 2015; Farzan Bortoletto 2022). Moreover, this was observed when S1-TMS was delivered at 150 ms, but not at 20 ms, after touch onset, indicating that TaMS activation involves S1 in the high-order phase of visual touch processing. This result supports the findings of previous studies (Bolognini et al. 2014; Pisoni et al. 2018) that identified 150 ms as the timing of TaMS activation during touch observation.

Notably, the results of the preregistered analyses of the TMS-EEG recordings show no evidence of alterations in TaMS connectivity in pw-BPD, but, together with exploratory findings, they rather suggest a possible impairment within the somatosensory network. Specifically, we did not observe any difference in TEPs between pw-BPD and HCs during touch observation, neither when they were directed towards a body part nor an object.

Considering that TEPs were not recorded at rest but during the observation of touches, we also analyzed the difference between TEPs and ERPs (i.e., ΔTEP-ERP) to disentangle the contribution of the processing of the stimuli, as indexed by ERPs, from the S1-connectivity pattern, as indexed by TEPs. This procedure allowed for a comparison between different ISIs without confounding factors, and the analysis of component peaks enabled us to include all relevant control conditions (i.e., group, stimulus, and ISI) in a single statistical model. Results on ΔTEP-ERP peaks revealed a lower P60 amplitude in pw-BPD compared to HCs irrespective of the ISI and of the visual stimulus, suggesting a general alteration in S1 connectivity in BPD. The P60 may reflect a secondary activation of the right sensorimotor areas (i.e., following the primary activation owing to the TMS pulse). Indeed, the topographical pattern of the P60 showed positive activity over the right centro-parietal electrodes. Previous studies stimulating M1 have localized it in parietal areas (Zazio et al. 2021) and associated it with the somatosensory reafference of motor-evoked potentials (Petrichella et al., 2017). Therefore, we hypothesize that the same circuit in the sensorimotor network would be activated following S1 stimulation. Moreover, Pisoni et al. (2018) attributed the same component (called P50) to vicarious S1 reactivity during the observation of human-directed touch. Although extremely intriguing, this hypothesis remains speculative, as we did not observe a difference at this latency between the observation of touches on a body part and on an object. One possibility that cannot be ruled out is that the P60 alteration reflects the non-specific effects of pharmacological treatments, as it does not interact with the ISI or the visual stimulus. However, it is worth noting that the rMT did not differ between pw-BPD and HCs, and that this TEP difference was specific for the P60 and not for other TEP components, indicating that the effect on the P60 cannot be attributed to general differences in cortical excitability. Consistently, results from TEPs recorded during real touches also indicated a perturbation of the somatosensory network in pw-BPD. Indeed, the difference in TEPs between pw-BPD and HCs during real touches was present when TMS was delivered 150 ms but not 20 ms after the real touch (i.e., the timing of S1 activation following somatosensory afference (Cohen et al. 1991) and affected late components (i.e., 100 ms from the TMS pulse on), suggesting that the alteration affects the higher-order stages of touch processing and S1 connections with distant areas, respectively (Bortoletto et al. 2015; Farzan Bortoletto 2022). Although late TEP latencies are known to overlap with the sensory processing of auditory and somatosensory components of the TMS pulse (Nikouline et al. 1999; Herring et al. 2015; Conde et al. 2019; Niessen et al. 2021), it is unlikely that sensory contamination explains the present findings. Indeed, in the within-subject comparisons, the stimulation parameters remained constant across all conditions. Conversely, if the TMS pulse had been perceived differently between groups, we would expect this to affect all between-subject comparisons, which was not the case. In support to this hypothesis, results from self-report questionnaire on subjective sensations associated with TMS showed no differences between groups. Another intriguing possibility is that such TEP components may involve subcortical structures, as late EEG components elicited by deep cortical stimulation have been recently linked with cortico-thalamo-cortical interactions (Claar et al. 2023). It is important to note, however, that interpretations on TEPs remain speculative, and rather than being conclusive, they could serve as hypotheses to be tested in future research.

Finally, results from ERPs during the observation of touches did not reach the threshold for significance in between-group differences, again providing no evidence of TaMS alteration in the elaboration of visuo-tactile stimuli. On the other hand, ERPs proved to be sensitive to stimuli manipulation, as baselineERPs confirmed that touches on a hand and touches on a

leaf were processed differently in both groups, with only the hand eliciting the typical N170 component for body parts (Kovács et al. 2006). Moreover, consistent with previous studies, no difference in ERPs was observed after real touches, indicating no generalized dysfunction of basic somatosensation in pw-BPD (Malejko et al., 2018; Pavony and Lenzenweger, 2014). Interestingly, a recent study in which pw-BPD underwent a comprehensive psychophysical evaluation of different dimensions of touch perception showed impairments in tactile sensitivity, defined as the ability to detect a tactile stimulus on the skin in the absence of deficits in tactile acuity (i.e., the ability to discriminate between two tactile stimuli presented in close proximity to one another) (Cruciani et al. 2023).

Taken together, these findings indicate that the impairment within the somatosensory system that we observed throughout the behavioral and neurophysiological measures in pw-BPD presents specific alterations which need to be further explored and disentangled in future studies.

4.1 Limitations

The present study presents a few limitations. First, a potential confounding factor is the pharmacological treatment present in most individuals with BPD in the study, which could not be statistically controlled in our sample due to the variability in treatments across patients. On the other hand, excluding participants on medication would significantly reduce the representativeness of the sample, as medication use is prevalent among patients in clinical settings. Second, the relatively small sample size may have reduced statistical power and limited the generalizability of the findings, also considering the exclusion criteria we introduced for TMS safety and experimental reasons. The sample size was carefully determined based on the expected effect sizes from the available literature on empathic levels in individuals with BPD. However, no prior studies exist on TMS-EEG recordings or the VTSC task in this population. Additionally, ethical considerations surrounding the recruitment of a clinical population warranted the use of a smaller sample for this exploratory phase. The data and results presented here can also serve as a foundation for more accurate sample size estimates in future studies. Finally, in all the visual touch trials, hands and leaves were touched by one hand, which may trigger additional mirroring mechanisms in sensorimotor cortices driven by action observation network recruitment with a time course similar to that of the TaMS (Guidali et al., 2023; Valchev et al., 2016), even in the object control trials. To boost the contrast between touches on hands and objects, future studies may use an object (e.g., a stick) to represent the visual touch.

5. Conclusion and future directions

The present study supports previous findings on empathic dysfunction in BPD and provides novel insights into the characterization of the somatosensory network during touch observation and perception. The observed alterations in behavioral as well as S1-connectivity measures provided by TEPs appear to reflect a disruption within the somatosensory network, rather than being specific to its visuo-tactile mirroring properties. While our findings do not provide definitive evidence regarding the integrity of TaMS in pw-BPD – leaving open the possibility that subtle alterations may have been missed or could emerge under different conditions – these results could inform treatment strategies by considering the somatosensory component

as a potential target. Indeed, current psychotherapies for BPD are primarily based on top-down interventions, while our findings suggest that bottom-up approaches, such as the sensorimotor therapy (Gene-Cos et al. 2016), may also be promising. However, further research is required to clarify the origin of the observed effects and their relationship with deficits in empathic abilities.

Authors' contribution

AZ: conceptualization, investigation, data curation, methodology, formal analysis, visualization, writing - original draft, project administration, funding acquisition; supervision; CML: investigation, formal analysis, writing - original draft; AS: methodology, formal analysis, software, writing - review and editing; GG: conceptualization, investigation, software, visualization, writing - review and editing; EM: investigation, writing - review and editing; DL: investigation, writing - review and editing; SM: resources, writing - review and editing; RR: resources, writing - review and editing; NB: conceptualization, writing - review and editing; MB: conceptualization, writing - original draft. All authors have approved the final article.

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Declarations of interest

None.

Data availability statement

The visual stimuli used in the present study and the analysis pipeline for TMS-EEG data have been uploaded in OSF together with the preregistration. Demographic data, individual responses from empathic questionnaires, performance on the VTSC task and TMS-EEG recordings are available in an online repository (doi.org/10.5281/zenodo.11244007; Aim 1).

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Figure Legends

Figure 1. Schematic representation of trials of the visuo-tactile spatial congruency (VTSC) task and the transcranial magnetic stimulation and electroencephalography (TMS-EEG) recording. **A)** VTSC task. Example of a congruent trial with visual touches on the right during the Hands block (left) and the Leaves block (right), showing the visual frames of the approaching hand towards the hands (or the leaves) with relative temporal durations, and the real touch delivered 10 ms after visual-touch onset. In incongruent trials with the same visual touches on the right, real touch was delivered on the left hand. Analogous trial types were also presented for visual touches on the left, and the block order was randomized. **B)** TMS-EEG recording. Representation of TMS-trials during the presentation of touches (i.e., visual-touch on the hand, visual-touch on the leaf, or real touch), with the TMS pulse over the primary somatosensory cortex (S1) delivered 20 or 150 ms after visual touch or real touch onset. In half of the trials, TMS was not delivered; trial order was randomized. In A) and B), reported time intervals represent frame durations.

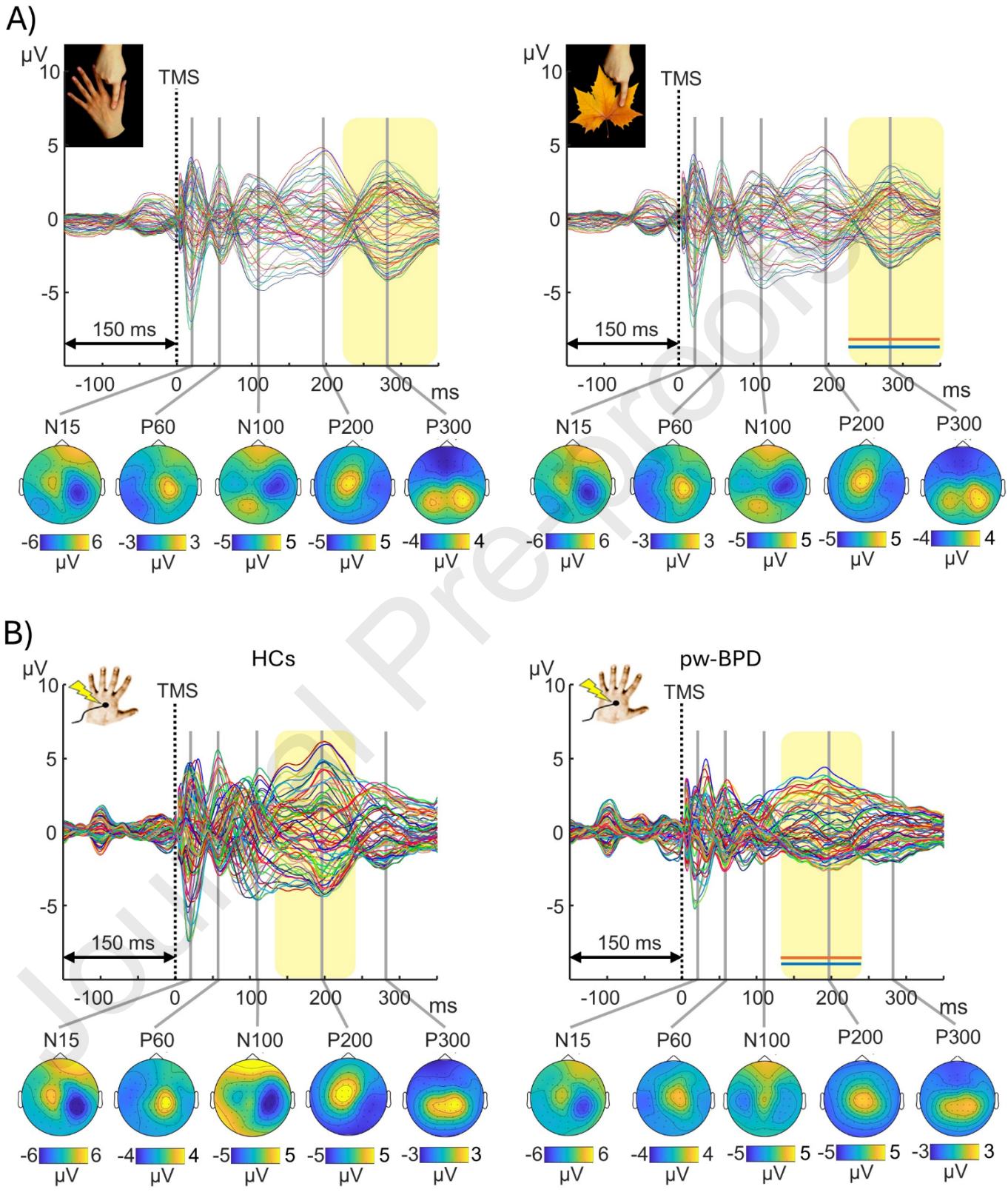
Figure 2. Flow diagrams for preregistered exclusion criteria. **(A)** For the visuo-tactile spatial congruency (VTSC), participants were excluded from statistical analyses in case they: did not complete all blocks of the VTSC session, their accuracy in catch 'no-tocuh' trials is below 50%, and/or reaction times (RTs) or number of errors in at least one condition deviated of more 2.5 standard deviations (SD) of the group mean. **(B)** For transcranial magnetic stimulation and electroencephalography (TMS-EEG) coregistration, participants were excluded from statistical analyses in case they: required a stimulation intensity (set at 110% of individual resting motor threshold, rMT) below 90% of the maximal stimulator output (MSO), their accuracy in catch trials is below 50%, the number of epochs left at the end of preprocessing is below 53 trials (i.e., 70% of the planned 77 trials).

Figure 3. Results of the questionnaires for empathic abilities. *Upper panel:* Questionnaire of Cognitive and Affective Empathy (QCAE); *lower panel*: Interpersonal Reactivity Index (IRI). In the box-and-whiskers plots, red dots indicate the means of the distributions. The center line denotes median values. Black dots show individual participants' scores. The box contains the 25th to 75th percentiles of the dataset. Whiskers extend to the largest observation, which falls within the 1.5 * inter-quartile range from the first/third quartile. The *p*-value of the significant group x empathy interaction is reported.

Figure 4. Main effect of stimulus in baseline event-related potentials (ERPs). Butterfly-plot ERPs generated by the sight of a hand (left panel) and of a leaf (right panel). Topographies (color bar reflects amplitude range) were obtained from the averaged signal between 160 and 180 ms after stimulus onset, and show the typical N170 pattern after the sight of a hand but not of a leaf. Horizontal lines indicate the latencies of significant clusters (orange: positive; blue: negative).

Figure 5 Transcranial magnetic stimulation evoked potential (TEP) results in trials with inter-stimulus interval (ISI)-150. **A)** Main effect of Stimulus: butterfly-plot TEPs generated 150 ms after visual touches on a hand (left panel) and on a leaf (right panel). **B)** Comparison between healthy controls (HCs; left panel) and patients with borderline personality disorder (pw-BPD; right panel) in TEPs generated 150 ms after real touches. Topographies (color bar reflects amplitude range) are shown for main TEP components. Horizontal lines indicate the latencies of significant clusters (orange: positive; blue: negative).

Figure 6. ΔTranscranial magnetic stimulation (TMS) evoked potentials (TEPs)-event-related potentials (ERPs) results. Butterfly plot of ΔTEPs-ERPs generated by primary somatosensory cortex (S1)-TMS delivered 150 ms (i.e., inter-stimulus interval (ISI)-150, upper row) and 20 ms (i.e., ISI-20, lower row) after visual-touch trials on the hand in HCs (left panel) and pw-BPD (right panel). Black thick traces indicate channel CP4, which was selected for peak detection. Vertical orange lines indicate the P60, for which we observed a main effect of group in the stimulus x ISI x group repeated-measures analysis of variance.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