Cortical plasticity of the tactile mirror system in borderline personality disorder

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Abstract

People with borderline personality disorder (BPD) show alterations in empathic abilities, which may involve automatic simulation processes relying on mirror-like mechanisms in the somatosensory domain. In the tactile mirror system, the observation of a touch on someone else's body activates a cortical network also involved in tactile perception, including the primary somatosensory cortex (S1). While alterations of mirror-like systems have been suggested in BPD, plasticity mechanisms within these systems are underexplored.

Here, we take advantage of a cross-modal paired associative stimulation (cm-PAS) protocol, a well-established non-invasive tool to induce brain plasticity, to shed light on possible neurophysiological alterations within the tactile mirror system in people with BPD.

The study will involve 24 participants diagnosed with BPD and 24 healthy controls in a 2-session experiment. Both groups will be evaluated in their empathic abilities by means of self-report questionnaires. Participants will undergo a tactile acuity test and a visuo-tactile spatial congruity (VTSC) task, in counterbalanced order, before and after a cm-PAS protocol in which an image of a hand being touched will be repeatedly paired with a transcranial magnetic stimulation (TMS) pulse over S1. The cm-PAS will differ between the two sessions in the time interval between the paired stimuli, i.e., 20 ms in the experimental session and 100 ms in the control session. The effects of the cm-PAS will be evaluated on tactile acuity, as an index of S1 activity, and on performance on the VTSC task, as an index of tactile mirror system functioning.

Introduction

Borderline personality disorder (BPD) is a mental health problem characterized by a pervasive pattern of impulsivity, self-image issues, difficulties in emotion regulation and unstable interpersonal relationships (Lazarus, Cheavens, Festa, & Zachary Rosenthal, 2014). Specifically, interpersonal dysfunctions are one of the main features of the disorder and have been associated with difficulties in mentalization as well as in the ability to empathize with others, with greater deficits in the cognitive dimension (i.e., understanding others' perspective) rather than in the affective dimension (sensing others' feelings; (Harari, Shamay-Tsoory, Ravid, & Levkovitz, 2010; Martin, Flasbeck, Brown, & Brüne, 2017). It has been suggested that empathic abilities may involve automatic simulation processes relying on mirror-like mechanisms, not only in the motor domain but also in the somatosensory domain (Bolognini, Rossetti, Convento, & Vallar, 2013; Keysers & Gazzola, 2009; Keysers, Kaas, & Gazzola, 2010). In the so-called tactile mirror system (TaMS), the observation of a touch on someone else's body has been shown to activate the same cortical network involved in tactile perception, including the primary somatosensory cortex (S1; (Bolognini, Rossetti, Fusaro, Vallar, & Miniussi, 2014; Pisoni, Romero Lauro, Vergallito, Maddaluno, & Bolognini, 2018). Intriguingly, the activity of TaMS has been shown to correlate with measures of cognitive empathy in the healthy population (Bolognini, Miniussi, Gallo, & Vallar, 2013; Bolognini et al., 2014), thus suggesting the hypothesis that the difficulties in cognitive empathy observed in BPD patients may be associated with alterations in TaMS functioning.

While previous studies have suggested mirror system alterations in BPD (Mier et al., 2013; Sosic-Vasic et al., 2019), still little is known about the integrity of a basic neurophysiological mechanism such as brain plasticity within these systems. Considering that the development of mentalization and empathic abilities appears to rely on early associative learning and metaplasticity, it has been suggested that the pathophysiology of BPD may be associated with alterations in neuronal plasticity, mediated by N-methyl-D-aspartate (NMDA) neurotransmission; however, evidence is still lacking (Grosjean & Tsai, 2007). Importantly, the integrity of plasticity mechanisms may represent a critical factor for the effectiveness of therapeutic interventions (Mancke et al., 2018).

Paired associative stimulation (PAS) protocols represent a well-established tool to non-invasively induce brain plasticity effects in humans (Guidali, Roncoroni, & Bolognini, 2021; Stefan, Kunesch, Cohen, Benecke, & Classen, 2000; Suppa et al., 2017; Wischnewski & Schutter, 2016). To induce changes in synaptic efficacy, PAS protocols exploit the Hebbian learning rule and the concept of spike-timing dependent plasticity observed at the cellular level, namely that neural connections are strengthened (or weakened) in the case of repeated activations of the presynaptic neuron before the postsynaptic neuron (or vice-versa) in a critical time interval of a few tens of ms (Feldman, 2012; Hebb, 1949; Miller, 1996). In classical PAS protocols targeting the somatosensory system (S1-PAS), a peripheral electrical stimulus over the wrist (acting as presynaptic activation) is repeatedly paired with a transcranial magnetic stimulation (TMS) pulse over S1 in the contralateral hemisphere (acting as postsynaptic activation). Depending on the time interval between the two stimuli, the S1-PAS may induce long-term potentiation or depression (LTP- or LTD-like, respectively) effects, lasting up to 30 minutes after protocol delivery (Wolters et al., 2005). In addition to neurophysiological effects (i.e., somatosensory evoked potential modulation), these plastic mechanisms have also been

detected by exploiting behavioral measures of S1 functioning, such as tactile acuity (Litvak et al., 2007).

PAS protocols have also been used to target multisensory integration networks: here, the peripheral and cortical stimuli belong to different systems (Guidali, Carneiro, & Bolognini, 2020; e.g., Sowman, Dueholm, Rasmussen, & Mrachacz-Kersting, 2014; Suppa, Li Voti, Rocchi, Papazachariadis, & Berardelli, 2015). Recently, a cross-modal PAS (cm-PAS) has been developed in the visuo-tactile domain, with the aim of targeting the TaMS (Maddaluno, Guidali, Zazio, Miniussi, & Bolognini, 2020; Zazio, Guidali, Maddaluno, Miniussi, & Bolognini, 2019). Compared to classical S1-PAS, in cm-PAS the peripheral electrical stimulus on the wrist is replaced by a visual stimulus of a hand being touched. The efficacy of the cm-PAS in inducing LTP-like mechanisms has been shown in a series of experiments, consisting of an increase in tactile acuity that was specific for the time interval between the visual stimulus and the TMS (i.e., 20 ms and not 60 nor 100 ms), for the site of cortical stimulation (i.e., S1 and not the primary visual cortex), and for the content of the visual stimulus (i.e., a hand being touched and not a moving hand). Moreover, cm-PAS modulated a neurophysiological correlate of S1 activity, namely, the amplitude of the P40 component of somatosensory-evoked potentials increased after cm-PAS. Overall, these findings are consistent with the hypothesis that when seeing a human touch on someone else's body, S1 is recruited by mirror-like mechanisms and can be involved in plasticity mechanisms (Zazio et al., 2019).

Taking together the existing evidence, here, we aim to shed light on the neural basis of interpersonal dysfunction in BPD by bridging the gap between the literature on empathic alterations in BPD patients on the one hand and on the neurophysiological underpinnings of TaMS and its plastic properties in the healthy population on the other hand. Specifically, we will investigate the integrity of plastic modulations within the TaMS in BPD patients, by employing the previously described cm-PAS.

The present study will involve BPD patients and healthy controls (HCs) undergoing two sessions of cm-PAS, i.e., an experimental session and a control session with a different time interval between the paired stimuli. The two groups will be compared in the cognitive dimensions of empathic abilities, measured by means of a self-report questionnaire. To assess the effects of the cm-PAS, both groups will undergo a 2-point discrimination task (2-PDT) as a measure of tactile acuity, an index of S1 activity (Litvak et al., 2007), before and after the cm-PAS protocol. Moreover, to explore whether the effects of the cm-PAS are limited to S1 activity or extend to behavioral correlates of TaMS, both groups will also perform a visuo-tactile spatial congruity (VTSC) task before and after the cm-PAS protocol, to measure TaMS functioning (Bolognini et al., 2014).

The hypotheses of the present study are the following (see Study design template in **Table 1**):

I. BPD patients are expected to show reduced cognitive empathy compared to HCs, as measured by means of a self-report questionnaire, consistently with previous findings (Harari et al., 2010; Martin et al., 2017).
II. HCs are expected to show an improvement in tactile acuity after cm-PAS. This effect will be considered a positive control, as it supports the effectiveness of a PAS protocol relying on TaMS (i.e., cm-PAS) in inducing plastic mechanisms (Zazio et al., 2019).

III. The effects of cm-PAS are expected to extend to a behavioral measure of TaMS functioning, i.e., the VTSC task: the cm-PAS is expected to strengthen the association between visual touches and S1 activation, thus inducing a decrease in performance, arising from a greater interference in case of spatial incongruity between the visual and the real touches and/or a greater facilitation in congruent trials. Therefore, we hypothesize HCs to show a decrease in performance on VTSC task after cm-PAS, as indexed by a greater difference in reaction times (RTs) between incongruent and congruent trials. No effects are expected after the control session of cm-PAS.

IV. In BPD, we hypothesize an alteration of plasticity within TaMS. Considering the empathic alterations in BPD, the rationale is the following. On the one hand, the development of mentalization and empathic abilities appears to rely on early associative learning (Grosjean & Tsai, 2007), on the other hand, mirror system alterations associated with empathic dysfunctions have been reported in BPD; therefore, we hypothesize that the pathophysiology of BPD may be associated with alterations in neuronal plasticity within TaMS (Mier et al., 2013; Sosic-Vasic et al., 2019). Specifically, we expect a reduced or null effect of cm-PAS compared to HCs on tactile acuity and on VTSC task. No effects are expected after the control session of cm-PAS.

Materials and Methods

Participants

The study will involve 24 patients with a diagnosis of BPD and 24 HCs. Participants will be mostly locals: BPD patients will be recruited by the Unit of Psychiatry, and HCs by word of mouth from the general local population. BPD patients will be matched one-to-one with HCs for gender and age (with a tolerability of ± 2 years).

Pharmacological treatments will not represent an exclusion criterion per se, according to the latest TMS guidelines (Rossi et al. 2021). Nevertheless, participants will not be included in the study in case they take pharmacological treatments that decrease the epileptic threshold (e.g., clozapine, bupropion). Up to now, in the previous experience of the Research Unit of Psychiatry, only 3 out of 200 BPD (1.5%) patients were taking one of these two treatments; therefore, the sample included in the study will be representative of the BPD population.

All participants will be between 18 and 40 years old, right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971), with no contraindication to TMS (Rossi et al., 2021). The study will be conducted at the Neurophysiology Lab of the IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli (Brescia, Italy). It has received approval from the local ethics committee (reference number: Parere 65-2020), and it will be performed in accordance with the ethical standards of the Declaration of Helsinki.

Sample size estimation

The sample size estimation was performed for each hypothesis, and we considered the one resulting in the highest sample. In GPower (v. 3.1.9.7, (Faul, Erdfeldfer, Lang, & Buchner, 2007), we set a power of 90% and a level of statistical significance of 2%.

I. For the comparison between BPD and HCs in empathic abilities, the power analysis was based on preliminary data for another study collected by the authors at the IRCCS Fatebenefratelli in Brescia, where the experiment will take place, as the BPD group is likely to be representative of the patients that will be tested in the present study (not published yet; see pre-registration on Open Science Framework here). Cognitive empathy measured with the QCAE questionnaire has been compared between 18 BPD patients and 15 HCs. BPD patients showed lower cognitive empathy compared to HCs (d = 1.07). The estimated sample for a one-tailed independent t-test resulted in 21 participants per group.

II. Regarding the effects of cm-PAS on tactile acuity in healthy participants, we focused on the data collected in a previous study (Zazio et al., 2019; Experiment 1), which included the same cm-PAS conditions as in the present study, namely cm-PAS with an ISI of 20 ms, and a control condition of cm-PAS with an ISI of 100 ms. To estimate the power needed to detect the interaction effect of within-subject factors, we considered the difference in sensory threshold (d' values), i.e., $\Delta Post_{cm\text{-}PAS}$-$Pre_{cm\text{-}PAS}$, in the two PAS conditions (dz = 0.95) and tested power for a one-tailed paired t-test. The estimated sample resulted in 15 participants.

III. For the effects of cm-PAS on VTSC task performance, power analysis considered the same parameters described in hypothesis II. As there are no studies testing the efficacy of cm-PAS on VTSC, the effect size was determined based on previous findings of cm-PAS on tactile acuity. The effect size described for the effect of cm-PAS on tactile acuity (ηp^2 = 0.3; (Zazio et al., 2019) is similar to the one described in a previous study aiming at modulating VTSC performance, as indexed by RTs, by means of online TMS protocols (ηp^2 = 0.25 - 0.31; (Bolognini et al., 2014).,

IV. In the absence of previous studies testing plasticity within TaMS in BPD, to assess plasticity alterations we hypothesized a medium effect size (ηp^2 = 0.06). Based on previous data on HCs (Zazio et al. 2019), we considered a correlation between repeated measures of 0.7. The estimated sample size for a between-within interaction rm-ANOVA resulted in 22 participants per group. **While the use of *a priori* defined levels of effect size may be criticized, the one used here is much smaller than the ones observed in the field (see hypothesis III). While we cannot fully rule out the possibility that smaller effects may be missed, possible negative findings may indicate that alterations of the tactile mirror system are not that crucial for BPD.**

Taking together the results of the sample size estimation, the final sample will include 24 participants per group, to ensure a counterbalance of session and task order.

Clinical assessment

Patient recruitment and clinical assessment will be performed by the Research Unit of Psychiatry of the IRCCS Fatebenefratelli. Patients will be evaluated using the Structural Clinical Interview for DSM-5 (SCID-CV and SCID-PD) (First, Williams, Karg, & Spitzer, 2017) for the diagnosis of BPD. Patients will not be 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 symptoms will be assessed by means of the Zanarini rating scale for BPD (ZAN-BPD, (Zanarini, 2003)) and the Symptoms Check-list 90 Revised (SCL-90-R, (Derogatis, 1994)). Depressive symptoms will be evaluated with the Beck Depression Inventory II (BDI-II,

(Beck, 1988)), impulsiveness with the Barratt Impulsiveness Scale (BIS, (Patton, Stanford, & Barratt, 1995)), and alexithymia with the Toronto Alexithymia Scale (TAS-20, (Bagby, Taylor, & Parker, 1994)). Moreover, interpersonal functioning will be evaluated with the Interpersonal Problems (IIP, (Pilkonis, Kim, Proietti, & Barkham, 1996)), and attachment style will be assessed with the Attachment Style Questionnaire ((Feeney, Noller, & Hanrahan, 1994)). Finally, the Childhood Trauma Questionnaire (CTQ;(Bernstein & Fink, 1998)) will be administered for the assessment of traumatic experiences, and the Inventory of statements about self-injury (ISAS, (Klonsky & Glenn, 2009)) for the evaluation of self-harm. The outcome of scales and questionnaires will be reported in aggregated form for descriptive purposes, and possible missing data will not represent an exclusion criterion.

Exclusion criteria

Participants will be excluded in the following cases: they do not complete experimental sessions; the stimulation intensity in any session exceeds 90% of the maximal stimulator output (MSO); accuracy in catch trials during the cm-PAS in any session is below 50%; accuracy during the VTSC in tactile-only trials and/or catch trials is below 50%. Finally, at the group level, participants will be excluded in case in any block the dependent variables (see following paragraphs for further details) exceed ± **2.5** standard deviations (SD) of the group mean. If some participants are discarded due to the exclusion criteria, the number of recruited participants will be increased to reach a total of 24 analyzed subjects per group.
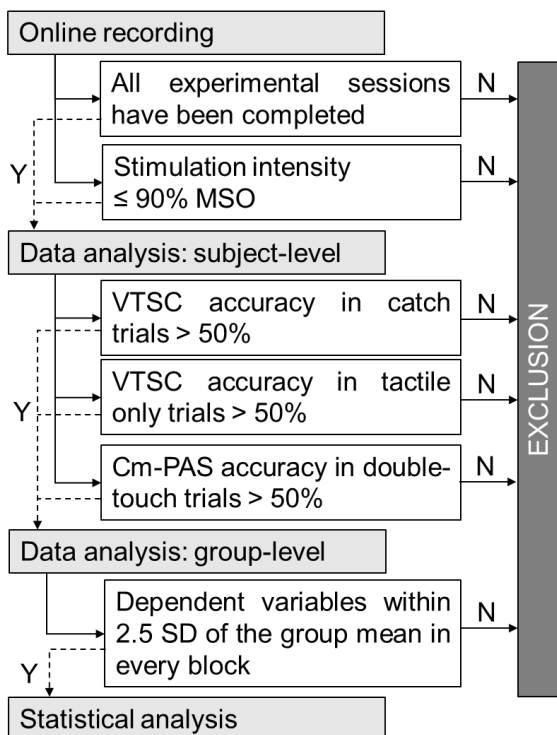
Figure 1. Flowchart of the experimental steps and the corresponding decisions for the inclusion of participants.

Design and procedure

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Participants will be involved in a two-session experiment, on separate days with at least 48 hours between them, at the same time of the day (i.e., in the morning or in the afternoon). Participants will be evaluated on their empathic abilities by means of a self-report questionnaire (see below) at the beginning of the first session. Then, the two sessions will differ only in the time interval for TMS delivery during the cm-PAS. In both sessions, before and after the cm-PAS protocol, participants will undergo a 2-PDT to test for tactile acuity and a VTSC task to test for tactile mirror system functioning, in counterbalanced order; within each participant, the same order will be kept before and after the cm-PAS and between sessions (**Figure 1**).
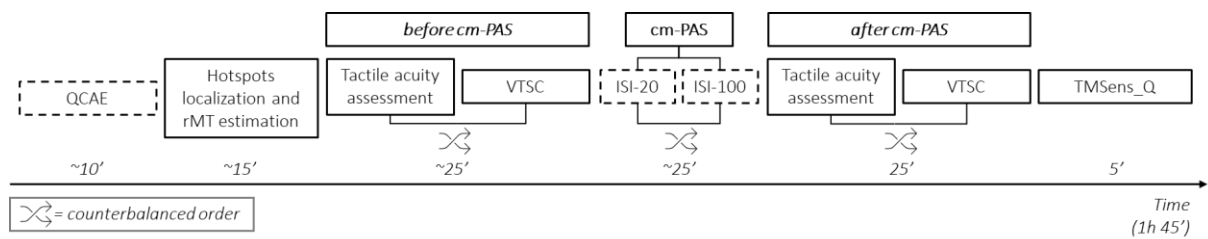
Figure 2. Schematic representation of the experimental session. First, participants will fill out the QCAE on their empathic abilities. Second, the motor hotspot will be localized, the resting motor threshold will be estimated, and then the S1 hotspot will be identified. Then, baseline performance at the tactile acuity and VTSC task will be recorded (in counterbalanced order), followed by the cmPAS with either an ISI of 20 or 100 ms (in separate sessions in counterbalanced order). Performance at tactile acuity and VTSC task will be recorded again within 30 minutes after the end of the cm-PAS, following the same order as in the baseline. Finally, participants will fill out a self-report questionnaire on sensations induced by TMS. Dashed panels: steps performed in one session only; continuous panels: steps performed in each session.

Questionnaire for empathic abilities

Participants will fill out a self-report questionnaire to assess their empathic abilities, namely, the Questionnaire for Cognitive and Affective Empathy (QCAE; (Di Girolamo, Giromini, Winters, Serie, & de Ruiter, 2019; Reniers, Corcoran, Drake, Shryane, & Völlm, 2011). The QCAE has already been administered in BPD patients (Grzegorzewski, Kulesza, Pluta, Iqbal, & Kucharska, 2019; Harari et al., 2010; Martin et al., 2017), and it has been proposed to overcome some intrinsic limitations of the Interpersonal Reactivity Index (Davis, 1983), another questionnaire on empathic abilities, both from psychometric (Chrysikou & Thompson, 2016) and theoretical (Michaels et al., 2014) points of view. As a dependent variable, we will consider the mean score given by the subscales 'perspective taking' and 'online simulation'.

Transcranial magnetic stimulation (TMS)

TMS will be delivered using a figure-of-eight coil (Magstim model Alpha B.I. Coil Range, diameter: 70 mm) and a monophasic Magstim 200^2 stimulator (Magstim, Whitland, UK). First, the motor hotspot for the abductor pollicis brevis (APB) muscle of the left hand will be identified in the right hemisphere as the highest and most reliable motor-evoked potentials with the same

TMS intensity. Second, the resting motor threshold (rMT) will be 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). This procedure will be performed for each participant at the beginning of each session. During this phase, electromyography will be visualized online by means of a bipolar belly-tendon montage of the APB of the left hand (g.HIamp, g.tec medical engineering GmbH, Schiedlberg, Austria). Then, right S1 will be localized 2 cm lateral and 0.5 cm posterior to the APB motor hotspot, according to (Holmes & Tamè, 2019; Holmes et al., 2019). During the stimulation of S1, coil orientation will be kept approximately at 45° from the midline, inducing a posterior-anterior current direction in the brain. Coil position will be monitored online using a neuronavigation system (Softaxic Optic 3.4; EMS, Bologna, Italy). Coil locations will not be saved. At the end of the **session**, participants will be asked to fill out a self-report questionnaire on the sensations induced by TMS (TMSens_Q, (Giustiniani et al., 2022)).

Cross-modal paired associative stimulation (cm-PAS) protocol

Cm-PAS will have the same parameters as those described in Zazio et al. 2019. Participants will be seated with their head on a chinrest to minimize head movements, at 57 cm distance from a computer monitor and will wear noise-cancelling earphones playing white noise, to attenuate the click-sound of the TMS. They will be asked to look at a red fixation cross that will be superposed to a left hand palm projected on the monitor in egocentric perspective. The hand will be repeatedly paired with a TMS pulse over the right S1. The time interval between the visual-touch onset and the TMS pulse will be 20 ms (cm-PAS$_{ISI-20}$) or 100 ms (cm-PAS$_{ISI-100}$), as in the original study (Zazio et al., 2019). TMS intensity will be set at 150% of participants' rMT, and 150 paired stimuli will be delivered at a fixed frequency of 0.1 Hz. To ensure that participants will be paying attention to visual-touch stimuli, they will be asked to detect rare events during the cm-PAS: in 15 randomly-presented trials, the visual-touch frame will be presented twice, and the TMS pulse will be paired with the defined ISI (i.e., 20 or 100 ms) on the second touch (**Figure 3A**). Participants will be asked to press a button on a computer keyboard with their right hand every time they will detect the double visual-touch trials. The number of correct detections will be recorded. The actual timing of visual-touch stimuli will be checked using a photodiode.

Trials randomization and timing of the stimuli will be presented under computer control using the software E-Prime (2.0, Psychology Software Tool, Inc.).

Visuo-tactile spatial congruity (VTSC) task

The VTSC task will be adapted from (Bolognini et al., 2014). Participants will be seated in the same position as during the cm-PAS, and will be asked to look at a red fixation cross at the center of a computer monitor while they are presented pictures of left- and right-hand palms in egocentric perspective. In visuo-tactile trials (n=120), another hand will appear from the upper part of the screen, touching either the left or the right hand palm. Ten ms after the visual touch onset, a tactile stimulus will be delivered either on the left or on the right hand palm by means of small solenoid tappers. Therefore, the real and virtual hands will not be in the same position, as in previous versions of the VTSC task (Bolognini, Miniussi, et al., 2013; Bolognini et al., 2014). The tactile stimulus will be either spatially congruent (n=60) or incongruent (n=60) to the visual-touch stimulus, in random order. Participants will be asked to report the location

of the tactile stimulus, i.e., on the left or on the right hand, as fast and accurately as possible by pressing one of two buttons on a computer keyboard. Moreover, unimodal tactile-only (n=60) trials will be presented as a check that participants are responding to tactile stimuli; finally, catch trials will be provided (n=20) consisting of a brief change in the color of the fixation asterisk from red to green, to control for participants' attention to the visual stimuli (see exclusion criteria paragraph and **Figure 2).** Further details on the timing of the visual stimuli are reported in **Figure 3B**. Before starting the experimental block, participants will undergo a few practice trials, performed before the cm-PAS only. The VTSC total duration will be approximately 8 min. The actual timing of visual-touch stimuli will be checked using a photodiode.

Both reaction RTs and accuracy (percentage of correct trials) will be recorded. For each participant and each trial type, trials with RTs exceeding ± 2 SD will be marked as outliers and discarded, after transforming the data in case of non-normality of the distribution (see Statistical Analysis for the normality assessment). For RTs, the difference between incongruent and congruent trials ($\Delta RTs_{incong-cong}$) will be considered as the dependent variable.

Trials randomization and timing of the stimuli will be presented under computer control using the software E-Prime (version 2.0, Psychology Software Tool, Inc.).

Two-point discrimination task (2-PDT)

The 2-PDT will be used to assess tactile acuity and will be administered before and after cm-PAS. The procedure will be adapted from (Zazio et al., 2019) and (L. K. Case et al., 2016; L. Case et al., 2017). Participants will be blindfolded with their left arm relaxed on the desk, while an experimenter will touch them on the thenar eminence of the left hand palm with either one or two plastic tips, using an aesthesiometer, in a 2-alternative forced-choice task. In a range between 3 and 15 mm, 13 distances will be tested in descending blocks of 6 trials, each block comprising 3 trials with 1 tip and 3 trials with 2 tips, in random order. This procedure will be repeated 2 times for a total of 12 trials for each distance tested (total number of trials: 156). A brief break will be provided at the end of each repetition or if requested by the participants. A first experimenter, who will be blind to the experimental session, will be trained to deliver tactile stimuli with a frequency of approximately 0.5 Hz and to always apply the same pressure. Participants will be asked to verbally respond (either 'one' or 'two') just after they have felt the touch, while a second experimenter will record their responses on a computer. To ensure that participants have understood the task and to make them familiar with the sensations, before starting the experimental procedure, a few examples of touches with either one tip or two tips with a 15 mm distance will be delivered, and feedback on their accuracy will be provided by the experimenter. The 2-PDT estimated total duration will be approximately 10 min.

Performance on the 2-PDT will be evaluated according to the signal detection theory (Green & Swets, 1966), which disentangles the contribution of perceptual sensitivity (*d'*) and response bias (*c*). Specifically, we will consider as a dependent variable the sensory threshold, defined as the distance in mm corresponding to 50% of performance. The sensory threshold will be estimated by fitting a logistic function to *d'* values (transformed to fit in a range between 0 and 1; (R Core Team, 2022). The fitting will be done in R using the 'fitting generalized linear models" (glm function, binomial family). If a participant shows negative values in the sensory threshold, she/he will be discarded from this analysis.
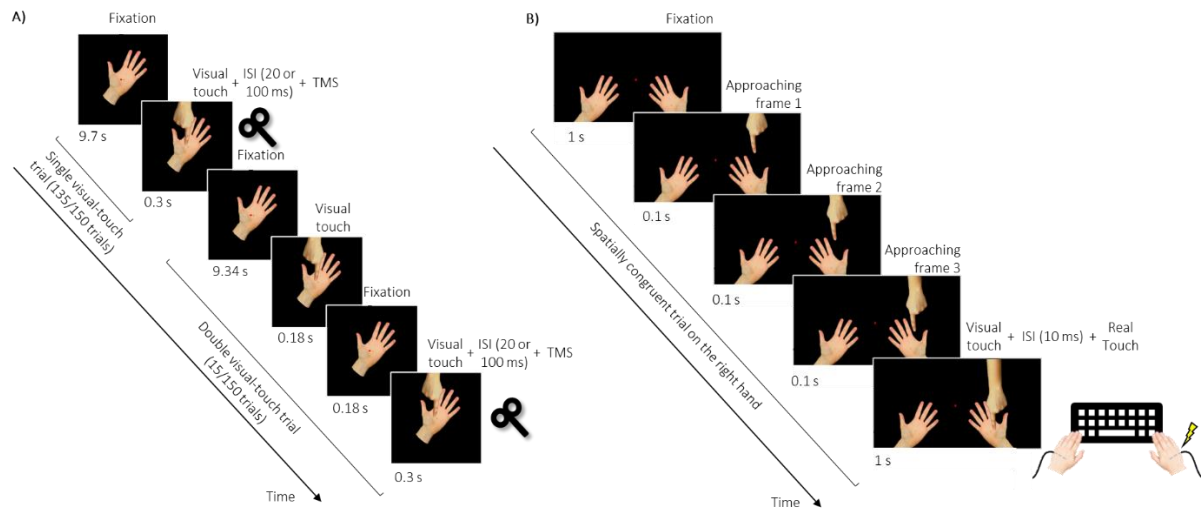
Figure 3. Schematic representation of the experimental paradigms. **A)** Cm-PAS trials: a single visual-touch trial followed by a double visual-touch trial. In single visual-touch trials (n=135), a fixation frame depicting a left hand palm will be presented for 9.7 s, followed by a visual-touch frame for 300 ms in which a hand in an allocentric perspective overlaps the hand palm in an egocentric perspective. After that, a new trial begins without interruption, thus giving the illusion of an apparent motion of the hand touching the hand palm. In double visual-touch trials (rare events, n=15), the fixation frame will be presented for 9.34 s, followed by a visual touch frame (180 ms), a fixation frame (180 ms) and a second visual touch frame (300 ms), thus giving rise to an apparent motion of a double touch on the hand palm. In both trial types, the TMS pulse will be delivered after the visual touch trial lasting 300 ms, with a time interval of 20 ms (cm-PAS$_{ISI-20}$) or 100 ms (cm-PAS$_{ISI-100}$), in counterbalanced sessions. Participants will be asked to maintain fixation on the red asterisk in the center of the palm in the same location where the visual touch will occur. **B)** Example of a spatially congruent trial in the VTSC task. A fixation frame is presented for 1 s, depicting a left hand and a right hand in an egocentric perspective. Then, 3 approaching frames of 100 ms each will be presented, showing the hands as in the fixation frame and another hand appearing from the upper part of the screen getting closer to the right hand. Finally, a visual touch stimulus will be presented for 1 s, in which the hand in an allocentric perspective overlaps the hand palm in an egocentric perspective. The whole sequence within each trial gives the impression of an apparent motion terminating with a visual touch on the hand. Ten ms after the visual touch trial, a real touch will be delivered on the participants' right hand-palm. The same trial structure applies to spatially congruent trials on the left side and to spatially incongruent trials. In unimodal tactile-only trials, participants will be shown with the two hands in an egocentric perspective, and only a tactile stimulus will be delivered (thus, participants will have to provide a response, which will be independent from visuo-tactile integration).

Planned Statistical Analysis

Statistical analysis will be performed in Jamovi (v. 2.3.21; Study Design Template in **Table 1**). Statistical significance will be set at $p < 0.02$.

I. First, BPD patients and HCs will be compared in cognitive empathy levels obtained from the QCAE by means of a one-tailed Yuen's trimmed mean t-test, a robust version of the t-test for independent samples (Mair & Wilcox, 2020).

II. Second, as a positive control, tactile acuity sensory threshold will be analyzed in HCs by means of a repeated-measure analysis of variance (rm-ANOVA) with factors Time (Pre$_{cm-PAS}$, Post$_{cm-PAS}$) and ISI (ISI-20, ISI-100).

III. Moreover, to assess the effects of cm-PAS on VTSC task performance in HCs, a rm-ANOVA with factors Time (Pre_{cm-PAS}, $Post_{cm-PAS}$) and ISI (ISI-20, ISI-100) will be performed on $\Delta RTs_{incong-cong}$.

IV. Finally, the two groups will be compared in the effects induced by the cm-PAS on tactile acuity sensory threshold and VTSC task performance (RTs). The analyses will consist of a 2x2x2 mixed-design ANOVA with between factor Group (BPD, HCs) and within factors Time (Pre_{cm-PAS}, $Post_{cm-PAS}$) and ISI (ISI-20, ISI-100).

Normality of continuous data will be assessed by means of Shapiro-Wilk test. Whenever deviating from normality, data will be transformed according to the commonly used transformations for continuous data, as there is no robust version of rm- or mixed-design ANOVA: square root, i.e., $\sqrt{}$(raw data); base-ten logarithmic, i.e., log10(raw data), and (c) inverse transformation, i.e., 1/(raw data). To account for possible negative values, as well as values between 0 and 1, when applying these transformations, we will add a constant to the raw data values, thus anchoring the minimum of our distribution(s) to 1 (Osborne & Carolina, 2016). **Then, the transformation showing the best fit to a normal distribution will be assessed as the shortest Euclidean distance from a normal distribution, according to Cullen-Frey graphs and the 'fitdistrplus' package in R (Delignette-Muller & Dutang, 2015); https://cran.r-project.org/web/packages/fitdistrplus/index.html).** If none of these transformations makes the data distribution close enough to normality, i.e., **the transformed distribution presents values of an excess kurtosis (beyond 3 ± 2) and square of skewness > 1 on Culley Frey graph (George & Mallery, 2019)**, we will proceed with non-parametric tests.

While the analyses described above are the ones that will drive the interpretation of results and the conclusions, results will also be supported by equivalent tests using Bayesian statistics, performed in JASP (v. 0.17.1.0).

Question	Hypothesis	Sampling plan	Analysis Plan	Rationale for deciding the sensitivity of the test for confirming or disconfirming the hypothesis	Interpretation given different outcomes	Theory that could be shown wrong by the outcomes
I. Do BPD show alterations in their empathic abilities?	Cognitive empathy: BPD < HCs. BPD patients will show lower cognitive empathy levels (i.e., mean score given by the subscales 'perspective taking' and 'online simulation') compared to HCs, as assessed by means of QCAE.	Power analysis based on preliminary data collected by the authors for another study (not published yet; see OSF preregistration here). Cognitive empathy measured with the QCAE has been compared between 18 BPD patients and 15 HCs. Power analysis has been performed in GPower (v. 3.1.9.7, Faul et al. 2007), with a power of 90% and a level of statistical significance of 2%. BPD patients show lower cognitive empathy compared to HCs ($d = 1.07$). The estimated sample for a one-tailed independent t-test resulted in 21 participants per group.	24 BPD patients and 24 HCs will be compared in cognitive empathy levels obtained from the QCAE by means of a one-tailed Yuen's trimmed mean t-test, a robust version of the t-test for independent samples (Mair & Wilcox, 2020).	The effect size for power analysis was determined based on preliminary data collected at the IRCCS Fatebenefratelli in Brescia (where the experiment will take place), as the BPD group is likely to be representative of the patients that will be tested in the present study.	Lower cognitive empathy levels in self-report measures in BPD patients compared to HCs will be interpreted as a difficulty in understanding others' mental states. If the two groups will not differ in the empathic abilities, it will be discussed whether the obtained results represent a non-replication of previous findings or a difference in the samples.	-

II. Is cm-PAS$_{ISI-20}$ effective in inducing plastic mechanisms in HCs, as indexed by tactile acuity? (positive control)	Improvement in tactile acuity after cm-PAS in HCs: cm-PAS$_{ISI-20}$ > cm-PAS$_{ISI-100}$. HCs will show a greater improvement in tactile acuity (i.e., *d'* sensory threshold) after the cm-PAS$_{ISI-20}$ compared to the control condition cm-PAS$_{ISI-100}$.	Power analysis based on previous findings on the effects of cm-PAS in HCs on tactile acuity (Zazio et al., 2019), performed in GPower (v. 3.1.9.7, Faul et al. 2007), with a power of 90% and a level of statistical significance of 2%. We considered the data collected in Experiment 1, which included the same cm-PAS conditions as in the present study. To estimate the power needed to detect the interaction effect of within-subject factors, we considered the difference in sensory threshold (d' values), i.e., ΔPost$_{cm-PAS}$-Pre$_{cm-PAS}$, in the two PAS conditions (effect size *dz* = 0.95) and tested power for a one-tailed paired t-test. The estimated sample resulted in 15 participants.	A rm-ANOVA with factors Time (Pre$_{cm-PAS}$, Post$_{cm-PAS}$) and ISI (ISI-20, ISI-100) will be performed on tactile acuity recorded in 24 HCs.	The effect size for power analysis was determined based on a previous study by Zazio et al. (2019), testing the effects of cm-PAS on tactile acuity in HCs, which included the same cm-PAS paradigm as well as the same control condition of the present study.	An interaction Time X ISI showing a greater improvement in tactile acuity after cm-PAS$_{ISI-20}$ compared to cm-PAS$_{ISI-100}$ will be interpreted as a successful replication of previous findings, supporting the efficacy of cm-PAS in inducing LTP-like mechanisms within the somatosensory domain. The absence of a Time X ISI interaction will not confirm the hypothesis, and hypothesis IV will not be tested.	-
III. Is cm-PAS$_{ISI-20}$ effective in inducing plastic mechanisms in HCs, as indexed by behavioral performance on VTSC task?	Decrease in performance (i.e., greater ΔRT$_{incong-cong}$) on VTSC task in HC after cm-PAS: cm-PAS$_{ISI-20}$ > after cm-PAS$_{ISI-100}$. HCs will show a greater decrease in VTSC task performance	Power analysis considered the same parameters described in hypothesis II.	A rm-ANOVA with factors Time (Pre$_{cm-PAS}$, Post$_{cm-PAS}$) and ISI (ISI-20, ISI-100) will be performed on VTSC measures recorded in 24 HCs.	The effect size for power analysis was determined based on previous findings of cm-PAS on tactile acuity, as there are no studies testing the efficacy of cm-PAS on VTSC. Nevertheless, a previous study using a similar VTSC task and using an online TMS protocol to induce modulations of performance (Bolognini et al., 2014), observed	An interaction Time X ISI showing stronger decrease in behavioral performance after cm-PAS$_{ISI-20}$ than after PAS$_{ISI-100}$ will support the efficacy of cm-PAS in inducing LTP-like plasticity mechanisms that extends to behavioral measures of TaMS functioning. The absence of a Time X ISI interaction will not confirm the hypothesis,	-

	after the cm-PAS$_{ISI-20}$ compared to the control condition cm-PAS$_{ISI-100}$.			significant effects on RTs with an effect size ranging between $\eta p^2 = 0.25$-0.31 for a rm-ANOVA interaction, which is similar to the one observed for tactile acuity in Zazio et al. 2019 ($\eta p^2 = 0.3$).	and hypothesis IV will not be tested.	
IV. Are plasticity mechanisms within the TaMS reduced in BPD patients?	Improvement in tactile acuity after cm-PAS: BPD < HCs. Decrease in VTSC task performance after cm-PAS: BPD < HCs. Compared to HCs, BPD patients will show reduced or null effect of cm-PAS, both on tactile acuity (i.e., *d'* sensory threshold) and performance on the VTSC task (i.e., $\Delta RT_{incong-cong}$).	Power analysis performed in GPower (v. 3.1.9.7, Faul et al. 2007) considered a medium effect size ($\eta p^2 = 0.06$), with a power of 90% and a level of statistical significance of 2%. Based on previous data on HC (Zazio et al. 2019), we considered a correlation between repeated measures of 0.7. The estimated sample size for a between-within interaction rm-ANOVA resulted in 22 participants per group.	24 HCs and 24 BPD patients will be compared in the effects induced by the cm-PAS on tactile acuity and on the VTSC performance, in separate analysis. The analyses will consist of 2x2x2 mixed-design analysis of variance (ANOVA) with between factor Group (BPD, HCs) and within factors Time (Pre$_{cm-PAS}$, Post$_{cm-PAS}$) and ISI (ISI-20, ISI-100).	In the absence of previous studies testing plasticity within TaMS in BPD, we hypothesized a medium effect size ($\eta p^2 = 0.06$).	An interaction Group X Time X ISI, showing differences between BPD patients and HCs in the effects of cm-PAS, will be interpreted as an alteration of the plastic mechanisms within the TaMS. The absence of an interaction with factor Group will not confirm the hypothesis.	-

Table 1. Study Design Template.

Authors' contribution

Funding

Conflict of interest statement

The authors declare that the research will be conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability statement

By the time of Stage 2 submission, the experimental data, the code, and the stimuli of the study will be made publicly available on an open access repository.

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