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Research paper

# Effect of metacognitive interpersonal therapy on brain structural connectivity in borderline personality disorder: Results from the CLIMAMITHE randomized clinical trial

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ABSTRACT

*Background:* Recently, we showed that Metacognitive Interpersonal Therapy (MIT) is effective in improving clinical symptoms in borderline personality disorder (BPD). Here, we investigated whether the effect of MIT on clinical features is associated to microstructural changes in brain circuits supporting core BPD symptoms.
*Methods:* Forty-seven BPD were randomized to MIT or structured clinical management, and underwent a clinical assessment and diffusion-weighted imaging before and after the intervention. Fractional anisotropy (FA), mean, radial, and axial diffusivities maps were computed using FSL toolbox. Microstructural changes were assessed (i) voxel-wise, with tract based spatial statistics (TBSS) and (ii) ROI-wise, in the triple network system (default mode, salience, and executive control networks). The effect of MIT on brain microstructure was assessed with paired tests using FSL PALM (voxel-wise), Linear Mixed-Effect Models or Generalized Linear Mixed Models (ROI-wise). Associations between microstructural and clinical changes were explored with linear regression (voxel-wise) and correlations (ROI-wise).
*Results:* The voxel-wise analysis showed that MIT was associated with increased FA in the bilateral thalamic radiation and left associative tracts ($p < .050$, family-wise error rate corrected). At network system level, MIT increased FA and both interventions reduced AD in the executive control network ($p = .05$, uncorrected).
*Limitations:* The DTI metrics can't clarify the nature of axonal changes.
*Conclusions:* Our results indicate that MIT modulates brain structural connectivity in circuits related to associative and executive control functions. These microstructural changes may denote activity-dependent plasticity, possibly representing a neurobiological mechanism underlying MIT effects.
*Trial registration:* ClinicalTrials.gov NCT02370316 (https://clinicaltrials.gov/study/NCT02370316).

## 1. Introduction

Borderline personality disorder (BPD) is a severe mental disorder characterized by affective instability, difficulties in emotional regulation, and deficits in metacognitive abilities (American Psychiatric Association, 2013). Psychotherapy is the recommended treatment, with pharmacotherapy as adjunctive component to address symptoms fluctuation during acute decompensation (American Psychiatric Association

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Practice Guidelines, 2001). Over the past 20 years, several psychotherapeutic approaches have been developed to treat BPD (e.g., Dialectical Behavioral Therapy, Transference Focused Psychotherapy, Mentalization-based treatment, Schema-focused therapy), which demonstrated clinical efficacy (Bateman and Fonagy, 2009; Fischer-Kern et al., 2015; Giesen-Bloo et al., 2006; Linehan et al., 2015). Recently, we demonstrated that Metacognitive Interpersonal Therapy (MIT), an approach targeting metacognitive abilities and interpersonal relationships, is effective in ameliorating these psychopathological variables as well as other clinical dimensions (Rossi et al., 2023). In terms of the possible neurobiological mechanism underlying response to intervention, we reported that patients receiving MIT showed a reduction in the right amygdala activation, potentially serving as a neural correlate of the improved emotional regulation (Rossi et al., 2023). This is in agreement with previous studies showing that the amygdala is hyperactive in BPD patients (Ruocco and Carcone, 2016) and that interventions normalizing its activity might be beneficial (Geurts et al., 2022; Goodman et al., 2014). In addition to functional dysfunction, patients with BPD show alterations in structural connectivity, i.e., the axonal fibers connecting cortical regions through the white matter (WM). Specifically, they show impairment in structural pathways supporting behavior and cognitive processes (e.g., corticolimbic and cortico-cortical tracts) (Gan et al., 2016; Nenadić et al., 2020; Ninomiya et al., 2018; Quattrini et al., 2019b; Salvador et al., 2016), as well as WM tracts connecting hubs of the salience network (SN), the executive control network (ECN), and the default mode network (DMN) (Quattrini et al., 2022). These networks form a so-called “triple network system” (Menon, 2011) whose impairment is associated to behavioral dysregulation in BPD (Quattrini et al., 2022). Another possible mechanism underlying the effect of MIT may thus involve the modulation of structural pathways, e.g. through activity-dependent plasticity, which mainly involves axonal myelination (Bonetto et al., 2021; de Faria Jr et al., 2021; Sampaio-Baptista and Johansen-Berg, 2017). Myelin is the lipid-rich sheath coveting the axons and serves to boost axonal conductance; in the central nervous system it is produced by oligodendrocytes during the neurodevelopment (innate myelination) and as an activity-regulated mechanisms (adaptative myelination) (Monje, 2018). In particular, neural activity may promote several oligodendrocytes-related processes, including alterations in myelin sheath length and thickness, which results in an increased conduction speed of impulses along the axon (Xin and Chan, 2020).

Axonal integrity and myelination can be assessed in vivo with diffusion tensor imaging (DTI), a mathematical model that measures the diffusivity of water molecules within tissues. DTI model can provide different metrics of WM microstructural integrity, i.e., fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), axial diffusivity (AD) (Alexander et al., 2007; Bihan, 2014; Mori, 2007). FA is mainly sensitive to the presence and directionality of axons and can also provide information about myelination, as axonal membranes and myelin hamper the free diffusion of water molecule (Beaulieu, 2002; Mori, 2007). MD is a general measure of microstructural organization, and has been related to neurite density and myelination (Genc et al., 2017). Finally, RD and AD values generally decrease during increases in axonal density, caliber, and myelin (Kumar et al., 2012; Winklewski et al., 2018). DWI studies from our and other groups mainly showed reduced FA and increased RD, MD, and AD in patients with BPD (Grottaroli et al., 2020). Previous DTI studies reported that cognitive training can modulate structural connectivity and behavior in cognitively normal individuals (Abend et al., 2019; Huber et al., 2018; Zhu et al., 2021) and patients with schizophrenia (Subramaniam et al., 2018). While similar evidence for BPD is currently lacking, it is reasonable to assume that similar changes might underlie clinical improvements following MIT.

In this study, we assessed the effects of MIT on brain microstructural integrity to shed light on the possible mechanisms underlying clinical improvement. MIT effects were tested (i) at whole-brain level and (ii) at the network level (i.e., triple network system). Based on our previous studies (Quattrini et al., 2022, 2019b), we predicted that MIT is associated with microstructural changes in corticolimbic tracts (e.g. anterior thalamic radiation [ATR]), and in networks associated to metacognition deficits and behavioral/emotional dysregulation (i.e., SN and ECN) (primary outcomes). We also explored the association between longitudinal changes of brain microstructural and clinical changes (secondary outcomes).

## 2. Methods

### 2.1. Participants

Participants were enrolled in the context of the CLIMAMITHE study (Clinical Trials.org identifier: NCT02370316), a longitudinal, multicenter, randomized clinical trial aimed to assess clinical and neurobiological effect of a MIT approach, compared to a structured clinical management (SCM). The CLIMAMITHE protocol was approved by the ethical committee of the IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli in Brescia (Italy) (Protocol number 67/2014). Eligibility was defined based on: (i) BPD diagnosis (DSM-IV-TR), (ii) age 18–45, (iii) informed consent (Supplementary Fig. 1). Exclusion criteria included: (i) a lifetime diagnosis of schizophrenia, schizoaffective disorder, substance abuse or addiction in the 3 months before enrollment, bipolar disorder, organic mental syndromes, dementia or cognitive impairment, and relevant neurological signs; (ii) pregnant or lactating women; (iii) patients receiving concurrent psychotherapy. Patients' recruitment was performed from September 2015 to January 2018 at 2 recruitment centers: (i) IRCCS Istituto Centro San Giovanni di Dio, Brescia (Italy); (ii) Third Center of Cognitive Psychotherapy – Scuola Italiana di Cognitivismo Clinico-SICC, Rome (Italy). All participants provided written informed consent in accordance with the Declaration of Helsinki. The full description of the study protocol is provided elsewhere (Magni et al., 2019; Rossi et al., 2023).

Participants underwent multidimensional clinical assessment. In particular, we assessed: BPD symptomatology with the Zanarini rating scale for Borderline Personality Disorder (ZAN-BPD) (Zanarini, 2003); emotional dysregulation with the Difficulties in Emotion Regulation Scale (DERS) (Gratz and Roemer, 2004); metacognitive abilities with the Metacognition Assessment Interview (MAI) (Semerari et al., 2012); personality disorders' criteria with Structured Clinical Interview for DSM-IV-tr Axis II Personality Disorders (SCID II) (First, 2015); state-psychopathology with the Symptoms Check-list 90 Revised (SCL-90-R) (Derogatis et al., 1977); depressive symptoms with the Beck Depression Inventory II (BDI-II) (Beck et al., 1988); impulsiveness with the Barratt Impulsiveness Scale (BIS) (Patton et al., 1995); interpersonal functioning with the Inventory of Interpersonal Problems (IIP-47) (Pilkonis et al., 1996); and alexithymia with the Toronto Alexithymia Scale (TAS-20) (Bagby et al., 1994).

Patients' medication was controlled by adapting the American Psychiatric Association guidelines to harmonize prescriptions (American Psychiatric Association Practice Guidelines, 2001; Magni et al., 2019). Dose and molecules were monitored and recorded every 6 months, and consultants were provided (Rossi et al., 2023).

#### 2.1.1. Randomization and treatment administration

Participants were the allocated to MIT and SCM groups using a pre-generated block (4 units, i.e., 2 per arm) randomization scheme developed by the statistician (CF). Each block of allocation was prepared in a sealed envelope (total, $n = 40$). Every 4 enrolled participants, 1 envelope was randomly selected. The final allocation included $n = 39$ BPD for each intervention, delivered in each recruitment center (Magni et al., 2019; Rossi et al., 2023) (Supplementary Fig. 1).

Psychotherapies have been administered for 1 year by 12 therapists with (i) 4-year training in psychotherapy (psychodynamic- or Cognitive-Behavior Therapy -oriented), (ii) at least 2 years of clinical experience

and (iii) at least 1 year of experience in BPD treating. More details on therapists training are available elsewhere (Magni et al., 2019; Rossi et al., 2023). Interventions have been administered at both recruitment centers: (i) the MIT targets general psychopathology of personality, following a five-phase approach focused on the increase of meta-cognitive functions (ability to monitor problematic mental states, integration of mental state current trends, ability to consider the representational nature of thoughts, awareness of dysfunctional interpersonal cycles, development of the sense of self-agency); (ii) the SCM represents a general psychiatric treatment for BPD, including a supportive approach (psychoeducation, problem-solving, explicit safety planning, medication review, and assertive follow-up for missed appointments) (Magni et al., 2019; Rossi et al., 2023). For both arms, the full intervention included (i) individual weekly session (50-mn), and (ii) group session (i.e., manualized metacognitive skill training and problem-solving group, for MIT and SCM, respectively; 20 sessions of 90-min spread over 6 months) (Magni et al., 2019; Rossi et al., 2023).

### 2.2. MRI protocol

A subgroup of 60 participants underwent a multimodal MRI protocol (DWI, 3D T1-weihgted, fMRI, and FLAIR), which was acquired on a 3 Tesla scanner equipped with a 64 channels RF head coil (Skyra Siemens, Erlangen, Germany) at the Neuroradiology Unit of the Spedali Civili Hospital (Brescia, Italy) (Supplementary Fig. 1). For the purpose of this study, only the DWI sequence was considered.

DWI were collected along sixty-four non-collinear gradient directions ($b = 1000$ s/mm$^2$) and five non-weighted directions ($b = 0$ s/mm$^2$) using an axial spin-echo EPI sequence (TR = 8300 ms, TE = 75 ms, voxel size = 2.0 × 2.0 × 2.0, FoV = 224 mm, slice thickness = 2 mm). In addition, five non-weighted EPI scans ($b = 0$ s/mm$^2$) were collected with reversed phase-encoding blips for distortions correction.

### 2.3. DWI processing

For the purpose of the present study, we selected all patients for whom baseline (BL) and follow-up (FU) DWI scans were available. For one participant, MRI technical issues emerged during the DWI acquisition, leading to 59 scans available at BL. Of these, 12 were excluded at FU due to drop-out, thus leaving 47 subjects with BL and FU scans (Supplementary Fig. 1).

Data processing was performed using FMRIB's Software Library (FSL) (http://www.fmrib.ox.ac.uk/fsl/, version 5.0.9; RRID:SCR_002823) (Smith et al., 2004). First, EPI images acquired with opposite directions were combined to estimate the susceptibility-induced distortions, as implemented in the *topup* tool (Andersson et al., 2003). Then, the DTI sequences were corrected for eddy current-induced distortions and subject movements using *eddy* (Andersson and Sotiropoulos, 2016). Then, FSL's automated quality assessment (*eddy_quad*) was conducted (Bastiani et al., 2019). We defined excessive movement as mean head motion >2 mm, and one patient (MIT) was excluded. For each subject, the diffusion tensor was estimated with DTIfit from FDT tool (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT), and the diffusion maps (FA, MD, RD, and AD) were created.

The longitudinal diffusion processing pipeline was used following a previously described optimized protocol (Engvig et al., 2012) for the Tract-Based Spatial Statistics (TBSS; https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS) (Smith et al., 2006). For each subject, the first brain-extracted $b = 0$ volume at baseline (BL) and follow-up (FU) were aligned and resampled to a common in-between halfway space using SIENA (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/SIENA) (Smith et al., 2004, 2002). SIENA automatically extracted the brain and the skull, which were then aligned each other using the skull images to constrain the registration scaling. Brain images of each timepoint were resampled to the halfway space, creating the halfway map and calculating the related deformation matrix. The deformation matrix was then applied to FA, MD, RD, and AD maps, to co-register each timepoint to the halfway map using FLIRT (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FLIRT) (Jenkinson et al., 2002; Jenkinson and Smith, 2001). The halfway FLIRT-registered FA images were averaged to create a subject-wise mid-space template. Each template was then processed using the standard TBSS pipeline (Smith et al., 2006). Briefly, TBSS identifies the most representative image to be used as target, computes the affine- and non-linear transformations warping each subject to the target image and then to the MNI space, and generates a mean FA map from all subjects. The mean FA map was thresholded (FA > 0.2) to create a binary skeleton mask for the statistical analysis. Finally, the halfway FLIRT-registered images (FA, MD, RD, AD) were smoothed (sigma = 2) and projected to the previously generated skeleton mask using TBSS.

For the triple network system analyses, the WM pathways connecting hubs of the SN (anterior [aSN] and posterior [pSN]), the DMN (dorsal [dDMN] and ventral [vDMN]), and the ECN (left [LECN] and right [RECN]), were identified using a probabilistic fMRI-guided normative atlas (Figley et al., 2015). For each network subcomponent, the corresponding WM probability map was thresholded at 5 % to exclude low probability voxels and then binarized. These masks were then overlaid to the spatially normalized individual DTI maps (FA, MD, RD, AD) normalized to MNI space with the TBSS procedure, and the mean values were finally extracted.

### 2.4. Statistical analyses

#### 2.4.1. Clinical and demographic features

Statistical analyses were conducted using the R software package v4.1.1 (R Foundation for statistical computing, https://www.r-project.org/) and the R studio GUI (http://www.rstudio.com/; version 1.3.1073; RRID:SCR_001905). The Student's *t*-test or the Wilcoxon-Mann-Whitney test (based on the data distribution) were used for continuous variable, while the Pearson chi-square test was applied for categorical variables. Statistical significance was set to $p < .05$. To compare clinical effects, the Cohen's *d* for paired samples (*lsr* package; https://cran.r-project.org/web/packages/lsr/index.html; 95 % confidence interval) between FU and BL scales' scores for MIT and SCM was applied.

#### 2.4.2. Whole brain voxel-wise analysis

Analyses of TBSS data were performed using Permutation Analysis of Linear Models (PALM) from FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/PALM) (Winkler et al., 2014). First, a two-sample unpaired test was conducted on BL data to assess potential between group differences at baseline. Then, to assess DTI changes after each intervention, effects of MIT and SCM were tested separately for each group using paired tests. Mean FA, MD, RD, and AD baseline values were included as covariates. To test the Group × Time interaction, maps of differences between FU and BL (Δ) were computed for each DTI modality and included in a two-sample unpaired *t*-test comparing MIT and SCM groups. All voxel-wise comparisons were conducted including FA, MD, RD, and AD modalities in the same model, running 500 permutations with tail approximation and the threshold-free cluster enhancement (TFCE) method. The statistical significance was set to $p < .05$, family-wise error rate (FWER) corrected over modalities ($n = 4$, i.e., FA, MD, RD, and AD) and contrasts ($n = 2$, i.e., for unpaired model, i.e., BL comparisons: MIT > SCM, SCM > MIT; for paired models, i.e., longitudinal comparisons within each intervention: BL > FU, FU > BL). Finally, to test the association between DTI and clinical changes, voxel-wise regression analyses were conducted between Δ maps and Δ scores of clinical scales. Regressions were restricted to voxels for whom the voxel-wise paired models resulted significant, running 500 permutations with tail approximation and the TFCE method. The statistical significance was set to $p < .05$, FWER corrected for the number of contrasts ($n = 2$, i.e., for positive and negative correlations). Only significant clusters of size $k > 100$ were then considered. Finally, for mean values extracted from significant

clusters, the Spearman's rank correlation test was conducted between Δ DTI metrics and Δ scores of cognitive tests (statistical significance set to $p < .05$).

#### 2.4.3. Triple network system ROI-wise analyses

For each timepoint and within each group, the presence of extreme outlier values was assessed using the 1.5 IQR criterion but none was excluded. A two-sample unpaired test (Student's t-test or the Wilcoxon-Mann-Whitney test, based on the data distribution) was conducted on BL data to assess potential between group differences at baseline. A Bonferroni correction for multiple comparisons over modalities (i.e., the number of DTI indexes, $n = 4$; corrected $< 0.012$) was applied. To assess DTI changes after each intervention, the Linear Mixed-Effect (LME) (*nlme* package; https://CRAN.R-project.org/package=nlme) (Pinheiro and Bates, 2006) or the Generalized Linear Mixed Models (GLMM) (*glmmTMB* package; https://CRAN.R-project.org/package=glmmTMB) (Brooks et al., 2017) for paired samples (based on the data distribution), including random slope and random intercept, were applied. Each DTI metric (FA, MD, RD, and AD) of each network (i.e., aSN, pSN, dDMN, vDMN, LECN, and RECN) was independently tested and included in the LME model as the dependent variable, while Time, Group, and Time × Group interaction were entered as independent variables. A Bonferroni correction for multiple comparisons for LME/GLMM models over contrasts (i.e. Time, Group, and Time × Group interaction, $n = 3$) and modalities (i.e., the number of DTI indexes, $n = 4$; total corrections, $n = 12$, $p$ corrected $< .004$) was applied. *Post-hoc* analyses were then conducted for results from significant models and using the Student's *t*-test or the Wilcoxon-Mann-Whitney test (based on the data distribution) for paired samples. The statistical significance was set to $p < .05$. To test the association between DTI and clinical changes, Δ values for metrics significantly impacted by interventions were computed. The Spearman's rank correlation test was then conducted between Δ DTI metrics and Δ scores of cognitive tests which significantly changed after interventions. Statistical significance was set to $p < .05$.

## 3. Results

Table 1 summarizes baseline features of BPD patients assigned to the MIT and to the SCM arm. The two groups were comparable for demographic, behavioral, clinical features, and pharmacological intervention ($p > .05$), except for the ZAN-BPD cognitive sector and STAXI-2 Anger/Trait scores that were slightly higher in the MIT group ($p = .02$ and $p = .04$, respectively). Clinical effects of both interventions are reported in Supplementary Table 1. Both groups showed a significant improvement after the intervention, with larger effect sizes for MIT than SCM (Supplementary Table 1).

### 3.1. Effects of MIT on structural connectivity: whole-brain voxel-wise analysis

At baseline, no differences emerged for whole-brain structural connectivity between MIT and SCM participants ($p > .05$, TFCE and FWE corrected). After the intervention, in the MIT group a significant Time-effect ($p < .05$, TFCE and FWER corrected) was detected on FA of the left inferior fronto-occipital fasciculus (IFOF; peak coordinates: −43,36,-10), bilateral ATR, forceps minor and left cingulum (Supplementary Table 2) (Fig. 1). No Time-effect was detected for MD, RD, and AD measures ($p > .05$, TFCE and FWER corrected). In the SCM group, no Time-effect on any DTI metric was detected ($p > .05$, TFCE and FWER corrected for all modalities). The Group × Time interaction was not statistically significant ($p > .05$, TFCE and FWER corrected).

Finally, no significant associations were reported for regression between Δ FA and Δ scores of clinical scales in the MIT group at a $p < .05$ TFCE and FWER corrected threshold. When considering an more lenient threshold ($p < .025$ TFCE, over number of contrasts), significant positive associations emerged in the MIT group between Δ FA and Δ MAI score

**Table 1**
Baseline features of BPD patients by intervention group.

| Features | MIT $M \pm SD$ [range] | SCM $M \pm SD$ [range] | Test value | *p* value |
|---|---|---|---|---|
| N | 23 | 23 | | |
| Demographic | | | | |
| Age, years | 28 ± 8 [18–46] | 31 ± 8 [19–45] | $W = 208$ | .21 |
| Sex. females, % | 91 % | 78 % | $X^2 = 1.52$ | .22 |
| Education, years | 13 ± 4 [8–18] | 13 ± 3 [8–18] | $W = 260$ | .92 |
| Clinical | | | | |
| Illness duration, years | 10 ± 6 [2−23] | 14 ± 9 [2–38] | $W = 193$ | .17 |
| SCL-90-R, total score | 192 ± 70 [72–317] | 183 ± 64 [68–289] | $t = 0.44$ | .66 |
| BIS-11, total score | 74 ± 14 [49–102] | 74 ± 11 [55–94] | $t = 0.21$ | .83 |
| DERS, total score | 128 ± 25 [82–170] | 125 ± 25 [77–170] | $t = 0.41$ | .69 |
| ZAN-BPD, total score | 17 ± 6 [7–33] | 16 ± 5 [8–28] | $t = 0.41$ | .68 |
| Affect sector | 7 ± 3 [2−13] | 7 ± 2 [5–11] | $W = 256$ | .86 |
| Cognition sector | 5 ± 2 [2–8] | 3 ± 1 [1–6] | $t = 2.63$ | **.02** |
| Impulsivity sector | 2 ± 1 [0–6] | 2 ± 2 [0–6] | $W = 252$ | .78 |
| Interpersonal sector | 4 ± 2 [1–8] | 4 ± 2 [1–7] | $W = 280$ | .74 |
| STAXI-2 Anger/State | 25 ± 12 [15–60] | 22 ± 10 [15–53] | $W = 281$ | .53 |
| Anger/Trait | 11 ± 12 [1–35] | 5 ± 8 [1–25] | $W = 344$ | **.04** |
| Anger expression/Out | 22 ± 4 [14–30] | 20 ± 6 [10−32] | $t = 1.76$ | .09 |
| Anger expression/In | 23 ± 5 [13−32] | 23 ± 5 [14–30] | $t = 0.25$ | .81 |
| Anger expression/ Index | 63 ± 9 [42–83] | 58 ± 14 [33–85] | $t = 1.43$ | .16 |
| Anger control/Out | 14 ± 4 [8–22] | 14 ± 5 [7–24] | $t = -0.13$ | .90 |
| Anger control/In | 16 ± 4 [8–24] | 18 ± 5 [11–28] | $t = -1.52$ | .14 |
| TAS-20, total score | 59 ± 12 [39–84] | 59 ± 11 [34–72] | $W = 246$ | .88 |
| IIP, total score | 2 ± 1 [0.7–3.4] | 2 ± 1 [1.3–3.1] | $t = 0.69$ | .49 |
| MAI, total score | 31 ± 7 [22–47] | 34 ± 7 [21–44] | $t = -1.52$ | .12 |
| Pharmacotherapy | | | | |
| Typical antipsychotic, % | 0 % | 0 % | – | – |
| Atypical antipsychotic, % | 22 % | 30 % | $X^2 = 0.06$ | .80 |
| SSRI, % | 27 % | 26 % | $X^2 < 0.01$ | .99 |
| SNRI, *n*% | 5 % | 17 % | $X^2 = 0.80$ | .37 |
| TCA, % | 0 % | 0 % | – | – |
| MAOI, % | 0 % | 0 % | – | – |
| Mood stabilizers, % | 57 % | 64 % | $X^2 = 0.98$ | .61 |
| Benzodiazepine, % | 36 % | 22 % | $X^2 = 0.57$ | .45 |

Values are reported as mean (M) ± standard deviation (SD) and range (minimum-maximum). *T*, *W*, and $X^2$ denote the Student's test, the Wilcoxon-Mann-Whitney test, and the Pearson's chi-square test values, respectively. *P* denotes their statistical significance. Significant results are reported in bold.
Abbreviations: MIT, metacognitive Interpersonal Therapy; SCM, structured clinical management; SCL-90-R, Symptoms Checklist-90-Revised; BIS-11, Barratt Impulsiveness Scale-11; DERS, Difficulties in Emotion Regulation Scale; ZAN-BPD, Zanarini Rating Scale for Borderline Personality Disorder; STAXI-2, State and Trait Anger Expression Inventory; TAS-20, Toronto Alexithymia Scale; IIP, Inventory of Interpersonal Problems; MAI, Metacognitive Assessment Interview; SSRI, Selective serotonin reuptake inhibitors; SNRI, Serotonin and norepinephrine reuptake inhibitors; TCA, Tricyclic antidepressant; MAOI, Monoamine oxidase inhibitors.

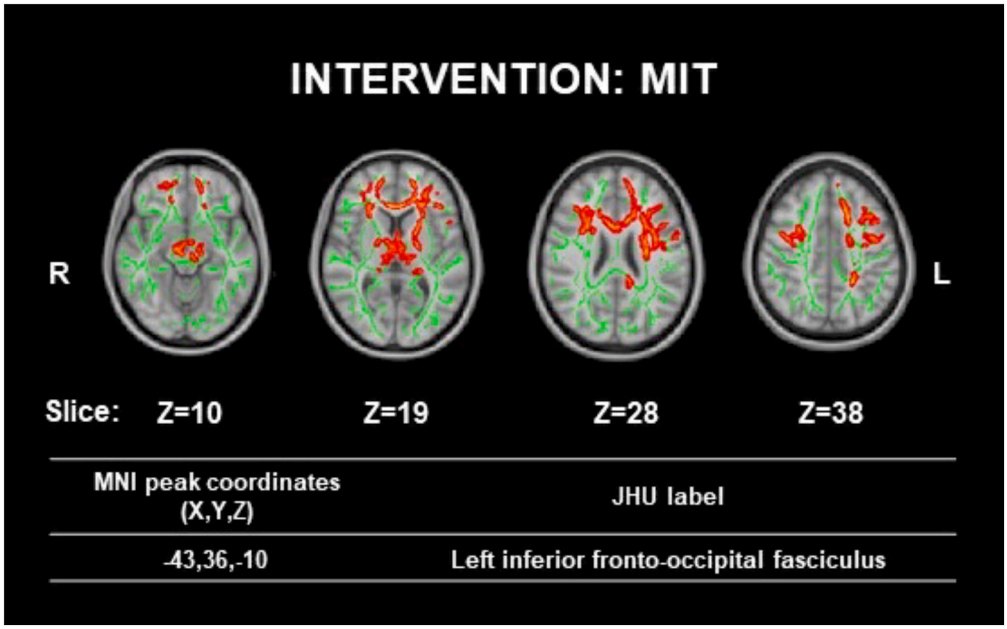


**Fig. 1.** Effect of Metacognitive Interpersonal Therapy (MIT) on fractional anisotropy (FA). Red-to-yellow voxels denote areas of increased FA after MIT intervention ($p < .05$, TFCE and FWER corrected). Voxels were thickened using *tbss_fill*, to aid visualization. No significant difference was observed after standard clinical management intervention. The standard Johns Hopkins University (JHU) white-matter tractography atlas was overlaid to the statistical map in order to identify the anatomical location of local maxima peak of significant clusters. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

($k = 894$; Fig. 2).

### 3.2. Effects of MIT on structural connectivity: triple network system ROI-wise analysis

At baseline, no differences emerged for the triple network system structural connectivity between MIT and SCM participants ($p > .012$, data not shown). After the intervention, LME models in the whole sample reported significant Time-effects for RECN (FA, $p = .029$) and LECN (AD, $p = .038$), but not surviving the multiple comparisons correction. Exploratory *post-hoc* analyses revealed a significant effect of MIT for the RECN FA ($p = .05$), and for both interventions for LECN AD ($p = .05$ and $p = .01$, for MIT and TCS, respectively). The Group × Time interaction was not statistically significant for any network ($p > .05$).

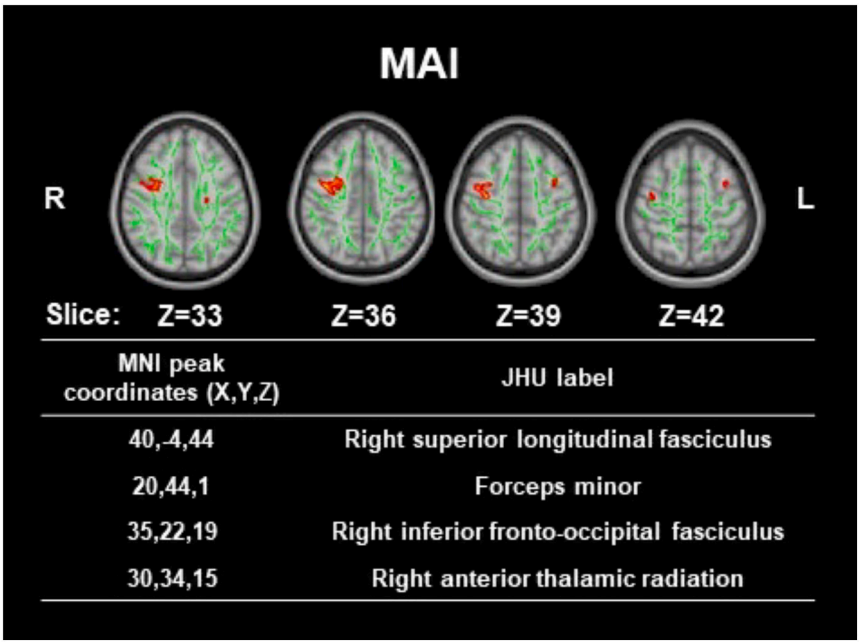


**Fig. 2.** Effect of metacognitive interpersonal therapy (MIT) on whole-brain fractional anisotropy (FA) of borderline personality disorder patients: results of voxel-wise regression. Significant positive associations between TBSS changes (Δ) of FA and clinical changes (Δ of scale scores) in the MIT arm were observed for Metacognitive Assessment Interview (MAI). Significant results ($p < .025$, TFCE, over the number of contrasts) were thickened using *tbss_fill*, to aid visualization. The standard Johns Hopkins University (JHU) white-matter tractography atlas was overlaid to the statistical map in order to identify the anatomical location of local maxima peak of significant clusters.

## 4. Discussion

We previously documented the clinical effectiveness of MIT in BPD (Rossi et al., 2023), but much remains unknown about the possible underlying neural mechanisms. Here, we reported that the clinical improvement after MIT was associated with increased FA in associative and executive control pathways. This pattern of microstructural changes is consistent with a mechanism of activity-dependent plasticity involving axonal myelination. Animal models of axonal injury with DTI showed that lower FA correlate with myelin injury at the cellular level, while the opposite pattern was observed during recovery, probably reflecting the effect of plastic reorganization (Harris et al., 2016; Lee et al., 2021; Yano et al., 2018). Studies on human neurodevelopment reported a progressive increase of FA in association with the progressive increase of cognitive functions, likely reflecting the effect of a protracted myelination due to activity-dependent plasticity mechanisms (Girault et al., 2019).

Our whole-brain analysis evidenced that patients receiving MIT reported increased FA in frontal-parietal WM pathways, which was associated to the improvement in metacognitive ability: (i) frontal portions of the bilateral ATR (connecting the anterior and dorsomedial thalamic nuclei with the frontal and anterior cingulate cortices), (ii) in left associative tracts, i.e., the IFOF (long-range pathway connecting the frontal lobes to parietal, occipital and temporal cortices), and the cingulum bundle (connecting temporal and the frontal areas), and (iii) the forceps minor (genu of the corpus callosum) (Martino et al., 2010; Radwan et al., 2022). Microstructural alterations of these pathways have been consistently described in BPD and associated to affective and behavioral dysregulation, and mood disturbances (Gan et al., 2016; Jenkins et al., 2016; Nenadić et al., 2020; Ninomiya et al., 2018; Quattrini et al., 2019b; Salvador et al., 2016; Vandekerckhove et al., 2020). Our results showing an improvement in the microstructural features of these tracts indicate that MIT is effective in restoring impaired pathways. Our results also proved the specificity of these effects: despite at uncorrected statistics, we found an association between increased FA and improvements in metacognitive abilities. We previously reported reduced microstructural integrity of the SN (Quattrini et al., 2022), and an association between lower functional connectivity in the SN and impaired metacognitive abilities (Quattrini et al., 2019a). In the present study, we did not detect any direct effect of MIT on the SN structural connectivity, which may indicate that MIT effects are not specific for this circuit. However, we note that the ATR is a WM tract connecting two hubs of the SN (Seeley et al., 2007), which may reconcile the apparent inconsistency with our previous results. A similar consideration may apply also to the IFOF, since this tract, particularly its frontal portion, has been associated to executive functioning and behavioral control (Leng et al., 2016; Waller et al., 2017). Interestingly, ATR, IFOF, and forceps minor have been suggested as part of a common pattern of WM alterations across several emotional disorders (e.g., bipolar disorder, major depressive disorder) (Jenkins et al., 2016), which are usually reported in comorbidity with BPD (Leichsenring et al., 2023). These pathways have been also proposed as inter-network connections, particularly the IFOF linking ECN to SN nodes (Jenkins et al., 2016; Waller et al., 2017). Our results thus suggest that MIT may primarily impact the inter-network structural connectivity within the triple network system.

Results from the triple network analysis were not statistically significant after multiple comparisons correction. We conducted a *post-hoc* analysis with an exploratory intent and found a bilateral effect of MIT on the executive control network, while the effect of TCS was limited to the left component. These results suggested that MIT was effective in improving the structural connectivity of the RECN, whose microstructural impairment was reported in BPD in our previous work (Quattrini et al., 2022). Results on LECN agree with our previous study on fMRI (Rossi et al., 2023), in which we reported similar effects of interventions on amygdala functional responses.

This work has some strengths. First, to the best of our knowledge this is the first study reporting structural connectivity changes following MIT intervention. We now provided complementary results to our previous report focused on functional activation changes (Rossi et al., 2023), thus returning a more complete framework of neural substrate of post-interventional changes. Our complementary analyses assessed neural changes both from an anatomical and a network-based perspective. This is especially relevant when considering the modular and integrative architecture of human brain, and the evidence that behavioral and higher cognitive functions are underpinned by specific network or by their interaction (Bertolero et al., 2015; Shirer et al., 2012).

### 4.1. Limitations

Our results should be also interpreted considering some limitations. First, DTI model has proven sensitive to several WM changes, but its metrics are not specific to myelin integrity. For example, while myelin might modulate the degree of anisotropy, diffusion anisotropy has been also described in non-myelinated nerves (Beaulieu, 2002; Beaulieu and Allen, 1994). It is likely that changes of DTI metrics might reflect the effect of complex interactions of multiple biological factors, including plasticity. Other in vivo techniques, which have shown higher specificity to myelin-related mechanisms (e.g., myelin water imaging), will be useful to investigate the nature of microstructural changes. Future studies would also benefit from the addition of biological assessments to further investigate the mechanisms of MIT. For example, DBT was previously reported to increased levels of brain-derived neurotrophic factor across different psychiatric populations, suggesting an effect on a key driver of plasticity (Mosiołek et al., 2023). Secondly, most WM voxels contain multiple fiber bundles in different orientations (e.g., crossing fibers, kissing fibers), which have been reported to affect water diffusivity direction (Choe et al., 2012; Figley et al., 2021; Wheeler-Kingshott and Cercignani, 2009). More advanced DWI models (e.g., diffusion kurtosis imaging, neurite orientation dispersion and density imaging) will be useful to provide more accurate estimates of diffusivity metrics and confirm our results. Finally, voxel-wise regression results were only significant at an uncorrected threshold. Future studies would be useful to confirm the association with clinical features. Finally, participants were generally under pharmacological treatments and we cannot exclude an effect of WM microstructure. However, given that patients were comparable for baseline medication, we can assume that our results were non significantly influenced.

## 5. Conclusion

We provided evidence of MIT effects on structural connectivity, which were suggestive of an underling activity-dependent plasticity involving axonal myelination. These changes affected mainly frontal-parietal pathways and may represent the neural substrate of improved behavioral regulation after MIT intervention. Finally, these results may provide evidence for the greater impact of MIT, compared with SCM, on general personality pathology, as noted in other work (Rossi et al., 2023), and support the idea that MIT is an effective treatment not only for BPD, but for general personality pathology.

## CRediT authorship contribution statement

**Giulia Quattrini:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Mariangela Lanfredi:** Writing – review & editing, Resources. **Giuseppe Nicolò:** Writing – review & editing, Resources. **Laura Pedrini:** Writing – review & editing, Resources. **Daniele Corbo:** Writing – review & editing, Resources. **Laura R. Magni:** Writing – review & editing, Resources, Data curation. **Andrea Geviti:** Writing – review & editing, Methodology, Formal analysis. **Clarissa Ferrari:** Writing – review & editing, Methodology, Formal analysis. **Antonio Semerari:** Writing – review &

editing, Resources. **Michela Pievani:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Roberta Rossi:** Writing – review & editing, Resources.

## Declaration of competing interest

The authors declare no conflict of interest.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2024.10.107.

## Data availability

The data supporting the conclusions of this study can be found in Zenodo: DOI: https://doi.org/10.5281/zenodo.11091556.

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