How Interpersonal Psychotherapy Changes the Brain:
A Study of fMRI in Borderline Personality Disorder

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ABSTRACT

Background: Recent guidelines and systematic reviews suggest that disorder-specific psychotherapeutic interventions are the first choice in the treatment of borderline personality disorder (BPD). The aim of this study is to examine brain activity changes in BPD patients (*DSM-5*) who received a revised BPD-adapted interpersonal psychotherapy (IPT-BPD-R) compared with patients on the waiting list.

Methods: Forty-three patients with a BPD diagnosis (*DSM-5*) were randomly assigned to IPT-BPD-R (n = 22 patients) or the waiting list with clinical management (n = 21 patients) for 10 months. Both groups were tested before and after treatment with the Social and Occupational Functioning Assessment Scale (SOFAS), the Clinical Global Impressions–Severity of Illness scale (CGI-S), the Borderline Personality Disorder Severity Index (BPDSI), the Barratt Impulsiveness Scale–version 11 (BIS-11), and the Autobiographical Interview. Both groups underwent pre- and posttreatment functional magnetic resonance imaging (fMRI) testing. The fMRI task consisted of the presentation of resolved and unresolved life events compared to a neutral condition. All structural and functional images were analyzed using Statistical Parametric Mapping 12 software, which interfaces with MATLAB. Clinical data were analyzed using analysis of variance for repeated measures. Patients were recruited between September 2017 and April 2019.

Results: In clinical results, for the 4 rating scales, a significant between-subject effect was found in favor of the IPT-BPD-R–treated group (CGI-S: $P = .011$; BPDSI: $P = .009$; BIS-11: $P = .033$; SOFAS: $P = .022$). In fMRI results, posttreatment versus pretreatment for the contrast unresolved life event versus neutral condition showed significantly decreased right temporoparietal junction (rTPJ: $x = 45$, $y = -51$, $z = 36$) ($P = .043$) and right anterior cingulate cortex (rACC: $x = -4$, $y = 37$, $z = 8$) activity ($P = .021$).

Conclusions: IPT-BPD-R appears to be effective in treating BPD symptoms, and these clinical effects are reflected in the functional changes observed with fMRI. Brain areas that showed modulation of their activity are the rTPJ and rACC, which are involved in mentalization processes that are fundamental to BPD pathology.

Trial Registration: Australian New Zealand Clinical Trials Registry (ANZCTR) code: ACTRN12619000078156.

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Borderline personality disorder (BPD) is a complex personality disorder that accounts for 6.4% of patients in primary care, 10% in outpatient psychiatric care and approximately 20% in inpatient psychiatric care.[1,2] It is a severe and heterogeneous psychiatric disorder mainly characterized by disturbed affectivity, lack of impulse control, disturbed interpersonal relationships, and diffuse identity.[3,4] The treatment of this complex disorder has always been a difficult challenge, and there are still open and debated questions among clinicians and researchers. Deficits in the regulation of internal and external states, which are one of the consequences of the lack of identity integration, respond partially to pharmacologic treatments and benefit more often from a psychotherapeutic approach.[5,6] Recent guidelines for the treatment of BPD[7–10] emphasize the central role of disorder-specific psychotherapeutic interventions in the treatment of this disorder.

Psychotherapy models that have been most commonly studied for BPD as single or combination treatments include dialectical behavior therapy (DBT),[11–13] mentalization-based treatment (MBT),[14] transference-focused psychotherapy (TFP),[15,16] cognitive therapy (CT),[17] schema-focused therapy (SFT),[18,19] and systems training for emotional predictability and problem solving (STEPPS).[20] In recent years, interpersonal psychotherapy (IPT) adapted for BPD patients (IPT-BPD) has been introduced as a tailored intervention for BPD in addition to the other specific psychotherapy models.[21–25] IPT-BPD has its roots in traditional IPT for major depression.[26] IPT-BPD was designed by Markowitz[21] to address the essential features of BPD and to alleviate the interpersonal problems typical of these patients. In recent years, we have proposed a revision of IPT-BPD—IPT-BPD-R—with a duration of 10 months.[27]

While, on the one hand, the clinical effects of available treatments for BPD have been widely studied, on the other hand, it is not yet clear how symptom improvement translates into changes in brain function of specific areas. In recent

Clinical Points

- Therapy for borderline personality disorder (BPD) is a challenge for clinicians. Interpersonal psychotherapy adapted to BPD–revised (IPT-BPD-R) is a manualized treatment focused on interpersonal problems that aims to improve specific BPD symptoms.
- Findings of the present study suggest the efficacy of IPT-BPD-R as single treatment of BPD patients and indicate that IPT-BPD-R modulates the activity of brain areas involved in the network of theory of mind and mentalization processes.

years, preliminary neuroimaging studies have indicated that BPD treatments target the brain level to achieve a therapeutic effect.[28] For example, DBT appears to modulate the neural basis of emotion regulation, whereas transference-oriented psychotherapy appears to down-regulate the neural circuitry of impulsivity.[29–36] Overall, the present findings suggest that disorder-specific psychotherapies affect brain function by down-regulating brain activity in limbic regions, particularly the insula and amygdala, and by differentially recruiting prefrontal areas, particularly the anterior cingulate cortex (ACC), orbitofrontal cortex, and dorsolateral prefrontal cortex (DLPFC), as well as through enhanced functional connectivity between limbic and prefrontal regions.[37,38]

To date, no study has examined the potential effects of IPT on brain activity in patients with BPD. Our research group conducted a previous functional magnetic resonance imaging (fMRI) study[39] to investigate the differences in brain function of BPD patients compared to those of healthy controls during an autobiographical memory task with exposure to resolved and unresolved life events. Results showed significant differences between the two groups during unresolved life events in terms of ACC, DLPFC, and temporoparietal junction (TPJ) activity.

The present fMRI study aims to investigate, in patients with BPD, the changes in brain activity of patients who received IPT-BPD-R for 10 months compared to patients who were on the waiting list (WL) during the same period.

METHODS

Participants

For this pre-post study, participants received a diagnosis of BPD according to *DSM-5* criteria.[40] Some of them (n = 24) were included in a previous fMRI study.[39] Patients were recruited at the Center for Personality Disorders–Department of Neuroscience, University of Turin, Italy, between September 2017 and April 2019. Patients with BPD had no comorbid psychiatric disorders. Exclusion criteria were delirium, cognitive and neurologic disorders, schizophrenia and other psychotic disorders, bipolar disorder, concomitant major depressive episodes, posttraumatic stress disorder, and drug use. Female patients of childbearing age were excluded if they were not using adequate contraceptive methods (according to physicians' judgment).

All participants (43 BPD patients) were randomly assigned to 1 of 2 independent groups: patients who received IPT-BPD-R (n = 22 patients) and patients on the waiting list (WL) with clinical management (CM; n = 21 patients). Participants did not receive any medication throughout the study period. Occasional use of benzodiazepines (lorazepam up to 2.5 mg/d, alprazolam up to 1 mg/d) and hypnotics (zolpidem up to 10 mg/d) was allowed in both groups up to 1 week before fMRI. The participating patients were outpatients who were not hospitalized during the study.

The 22 patients who received IPT-BPD-R and the 21 patients who were on the WL were matched for sex, age, and education (number of completed years of school and university as reported by the patients and confirmed by school and university transcripts). All participants had right-handed dominance with a range for the right-handedness laterality index (LI) $48 \leq LI\ 100$[41] and were aged between 18 and 60 years. Men and women were represented in both groups.

Psychotherapy was provided by 2 therapists trained in IPT-BPD with at least 2 supervised cases and 5 years of experience. Psychotherapy sessions were constantly supervised by a senior psychotherapist (S.B.) who checked compliance with the manual. Clinical visits were also monitored to ensure that patients' interpersonal disorders were not the focus. Treatment costs were covered by Italian Health Service.

Each patient voluntarily participated in the study after providing written informed consent. We adhered to the guidelines of the Declaration of Helsinki. Approval was obtained from the Ethics Committee of the University Hospital Città della Salute e della Scienza–Ospedale dell' Ordine Mauriziano in Turin. The study was registered in the Australian New Zealand Clinical Trials Registry (ANZCTR) under code ACTRN12619000078156.

Clinical Measures

Both groups (patients in IPT-BPD-R and patients in the WL/CM group) were tested by a clinician trained in assessment instruments (P.B.) before and after treatment or WL/CM with the following assessment instruments: the Social and Occupational Functioning Assessment Scale (SOFAS),[42] the Clinical Global Impressions–Severity of Illness scale (CGI-S),[43] the Borderline Personality Disorder Severity Index (BPDSI),[44] and the Barratt Impulsiveness Scale, version 11 (BIS-11).[45] To obtain life events for the fMRI task, all patients were assessed with the Autobiographical Interview (AI).[46]

The SOFAS is a clinician-rated scale to measure a patient's impairment in social and occupational domains. It is independent of the patient's psychiatric diagnosis and severity of symptoms. The score ranges from 0 to 100, with higher scores indicating better functioning.

The BPDSI is a semistructured clinical interview designed to assess the frequency and severity of symptoms related to BPD. The interview consists of 8 items rated on a 10-point frequency scale (0 = never; 10 = daily), including "abandonment," "interpersonal relationships," "impulsivity," "parasuicidal behavior," "affective instability," "emptiness,"

"angry outbursts," and "dissociation, and paranoid ideation," and 1 item rated on a 4-point severity scale that concerns "identity." The BPDSI demonstrated adequate reliability and construct validity.[47]

The BIS-11 is a 30-item self-report questionnaire that measures the trait of impulsivity on a 4-point Likert scale. Higher scores for each item indicate higher levels of impulsivity. Twelve items are reverse scored to avoid answer sets. Three factors can be determined: cognitive impulsivity, motor impulsivity, and non-planning impulsivity. The total score is the sum of these factors. The BIS-11 showed reasonable reliability and construct validity in both US[48] and Italian samples.[49]

The AI captures the entire life span, including interpersonal relationships with significant others. It is designed to capture 2 unresolved life events (1 with positive and 1 with negative content) and 2 resolved life events (1 with positive and 1 with negative content). The subject, together with the clinician, selected the significant life events. For each life event, the subject named 4 keywords that served as triggers for active recall during fMRI. In addition, the clinician provided a brief summary (word count between 25 and 27) for each event at the end of the interview. Four brief summaries and 16 keywords were collected for each subject by the AI to represent unresolved versus resolved life events during fMRI. We considered a resolved event to be a life event that the subject considered fully elaborated and completed, whereas we considered an unresolved event to be a life event that still had implications for the present and that the subject considered not fully integrated into his or her internal narrative.[39]

In addition, all subjects identified 4 neutral stories (word count between 25 and 27) with 4 keywords for the event before fMRI was performed. Summaries are used only to contextualize the event. Thus, they provide information pertaining to the context of all 4 keywords. The keywords indicate the meaning of the event: resolved, unresolved, and neutral. Events and keywords with a neutral meaning were selected from a predetermined set of neutral short stories. Special care was taken to ensure that the neutral stories did not contain social content and interpersonal interactions. A preliminary set of neutral stories[44] was previously presented to 130 subjects who indicated which stories and keywords they considered neutral. Only stories that were rated as neutral by 80% of the subjects were used as control conditions in the task (21 stories). Neutral stories did not involve autobiographical events.

Before fMRI, subjects were asked to check and confirm that each event was correctly assigned to resolved or unresolved experiences.

Interpersonal Psychotherapy Adapted for BPD–Revised

IPT-BPD-R consists of a 10-month therapy divided into 2 phases of 22 and 20 sessions, respectively. The duration of the sessions is 50 minutes. In the first phase (22 sessions), therapy aims to build a therapeutic alliance, limit self-destructive behaviors, and achieve initial symptom relief. The continuation phase (20 sessions) aims to maintain a strong therapeutic alliance, address distorted interpersonal dynamics, and develop more adaptive skills.

At the end of the 42 sessions, 3 more sessions may be offered if patients show serious difficulties in the discontinuation phase. In crisis situations, the therapist allows the patient 2 weekly contacts of 10 minutes by telephone. If needed, short-term hospitalization of 7–10 days may be considered. During hospitalization, IPT-BPD-R continues if the patient's clinical condition permits. Our revised model of IPT-BPD also includes an intervention for patients' family members to help them cope with their relative's illness.[27] Only outpatients who were not hospitalized during the intervention were included in this study.

Waiting List

BPD patients who did not receive psychotherapy were monitored with weekly clinical visits lasting 50 minutes. Symptoms reported by the patient were taken into account and managed with a supportive approach.

fMRI Task

Both groups underwent a pretreatment fMRI scan and a posttreatment fMRI scan. Approximately 10 months elapsed between the first and second runs. During each experimental fMRI session, we applied the task used in our previous study,[39] which intercepts hemodynamic responses in the brain regions of interest during the presentation of 2 types of events, resolved and unresolved. Each patient was instructed to recall resolved or unresolved content associated with each life event. The fMRI task included a control condition consisting of neutral events. Prior to each pre- and posttreatment fMRI experimental session, all patients received a training session in which we used a set of life events that differed from those used in the experimental sessions.

For the pre- and posttreatment fMRI runs, we used the same experimental procedure as in our previous study.[39] Each patient was presented with the same stimuli and the same fMRI task during both fMRI scans. The task was created using E-Prime software (Psychology Software Tools, Inc; Pittsburgh, Pennsylvania) to display the visual stimuli consisting of the text of the events for the conditions: resolved, unresolved, and neutral. The display system was supported by special glasses (Philips Resonance Technology, Inc). The fMRI task[39] consisted of 24 trials divided into 3 types of conditions: 8 resolved, 8 unresolved, and 8 neutral. All trials were pseudorandomized for each patient.

They were arranged in the following order: (1) summary (duration = 15 seconds), ie, brief summary of the life event; (2) fixation cross (duration = 5–6 seconds); (3) keyword (duration = 5 seconds); (4) fixation cross (duration = 6–7 seconds); and (5) response screen (duration = 4 seconds), in which all patients were asked to identify the emotion they experienced based on 3 possible responses: "positive," "neutral" or "negative." The last phase was used to check

Table 1. Comparison (with *t* tests and χ^2 tests) of Baseline Values for Demographic Variables Between the IPT-BPD-R and the WL/CM Groups[a]

Demographic Variable	BPD Patients in IPT-BPD-R	BPD Patients in WL/CM	t/χ^2	*P*
Age, y	35.37 ± 15.21	35.72 ± 14.94	0.542	.593
Men/women, n	7/15	8/13	0.186	.666
Level of education, y	13.40 ± 4.2	13.00 ± 3.75	0.941	.305

[a]Values are mean ± SD unless otherwise noted.
Abbreviations: BPD = borderline personality disorder, IPT-BPD-R = interpersonal psychotherapy adapted to borderline personality disorder–revised, WL/CM = waiting list plus clinical management.

Table 2. Comparison (With ANOVA) of Baseline Values for Rating Scales Measuring Symptoms and Functioning Between the IPT-BPD-R and WL/CM Groups[a]

Measure	BPD Patients in IPT-BPD-R Group	BPD Patients in WL/CM Group	ANOVA
CGI-S score	4.12 ± 0.86	4.27 ± 0.91	$F = 0.231$, $P = .619$
BIS-11 score	80.74 ± 9.80	81.39 ± 7.31	$F = 0.878$, $P = .384$
BPDSI score	49.03 ± 6.34	47.78 ± 6.85	$F = 0.560$, $P = .520$
SOFAS score	57.48 ± 7.21	56.21 ± 9.02	$F = 1.815$, $P = .192$

[a]Rating scale scores are shown as mean ± SD.
Abbreviations: ANOVA = analysis of variance, BIS-11 = Barratt Impulsiveness Scale–version 11, BPD = borderline personality disorder, BPDSI = Borderline Personality Disorder Severity Index, CGI-S = Clinical Global Impressions–Severity of Illness scale, IPT-BPD-R = interpersonal psychotherapy adapted to borderline personality disorder–revised, SOFAS = Social Occupational Functioning Assessment Scale, WL/CM = waiting list plus clinical management.

whether the task was performed correctly (for more details, see our previous study[39]).

fMRI Data Acquisition

All magnetic resonance images were acquired for pre- and posttreatment fMRI experimental sessions at the Center of Brain Imaging 3T-NIT–Hospital Città della Salute e della Scienza, Turin, Italy with a 3.0 T MRI Scanner (Philips Ingenia) equipped with a 32-channel array head coil. For each pre- and posttreatment fMRI experimental session, functional and structural images were recorded. For the acquisition of functional images we applied an Echo-Planar Image (EPI) sequence with the following parameters: TR/TE = 3,000/30 ms, 415 volumes, 32 slices, matrix size = 92 × 96, field of view = 224 × 224 mm^2, slice gap = 0.5 mm, slices aligned on the AC-PC line, flip angle = 90°. For the acquisition of structural images, we applied a T1-weighted sequence with the following parameters: TR = 8.1 ms, voxel size 1 × 1 × 1 mm^3, TI = 900 ms, TE = 3.7 ms.

fMRI Analysis

We analyzed all functional and structural images using Statistical Parametric Mapping 12 software (SPM12; Wellcome Department of Cognitive Neurology; London, UK)[50] interfaced on MATLAB (MathWorks; Cherborn, Massachusetts).

For each pre- and posttreatment fMRI experimental session, all images were preprocessed in line with our previous study (for details about the preprocessing procedure for realignment, coregistration, segmentation, and normalization, see our previous study[39]). After preprocessing, we performed the general linear model (GLM) for pre- and posttreatment fMRI runs for each patient.

At the first level, we convolved in the design matrix a stick function with a hemodynamic response function (HRF) to regressors of interest modeled in 3 contrasts: resolved keyword, unresolved keyword, and neutral keyword. To use a rigorous quality control check, we defined 6 parametric regressors of no interest to correct residual effects of head motion, and we excluded motion artifacts using the threshold > 2-mm translation and 2-degree rotation.

At the second level, to investigate how interpersonal psychotherapy modulates brain areas in BPD patients, we compared the 2 groups for posttreatment fMRI run versus pretreatment fMRI run using a full-factorial design, with the factor treatment group as independent between-subjects factor, the factor life-event at 3 levels (resolved keyword, unresolved keyword, neutral keyword), and the factor time (before and after treatment) as within-subjects factor.

We preliminarily computed the whole-brain exploratory analysis with a threshold of $P < .05$ family-wise error (FWE; see Supplementary Figure 1 and Supplementary Table 1).

Our a priori hypotheses were based on results of the previous study.[39] For this reason, we performed small volume correction (SVC)–based analyses using a SVC on the following coordinates centered with spheres of 10-mm radius: right anterior cingulate cortex (rACC, $x = 8$, $y = 39$, $z = 12$), left anterior cingulate cortex (lACC, $x = -10$, $y = 29$, $z = 12$), right dorsolateral prefrontal cortex (rDLPFC, $x = 41$, $y = 17$, $z = 30$), left dorsolateral prefrontal cortex (lDLPFC, $x = -37$, $y = 19$, $z = 26$), and right temporal parietal junction (rTPJ, $x = 42$, $y = -56$, $z = 34$). In addition, we computed the correlation between decrease of brain activity and improvement of BPD symptoms (decrease of BPDSI total score after treatment) for the contrast between unresolved condition and neutral condition in each group. The Spearman rank non-parametric (ie, Spearman ρ) correlations were calculated. In particular, we extracted contrast estimates at the first level and correlated those scores with BPDSI total score, applying the toolbox REX (http://web.mit.edu/swg/software.htm).

RESULTS

Sample Characteristics

The IPT-BPD-R (n = 22) and WL/CM (n = 21) groups were analyzed at baseline using *t* tests and χ^2 tests to compare age, sex distribution, and educational level. The results showed no significant differences between the groups (Table 1).

Analysis of variance was calculated between the 2 groups at baseline to compare scores on the 4 clinical rating scales: CGI-S, BIS-11, BPDSI, and SOFAS. Again, no significant difference was found in this analysis (Table 2).

Three subjects in the IPT-BPD-R treated group (13.63%) and 4 subjects in the WL/CM group (19.05%) discontinued the study in the first month because they did not comply with the study protocol.

Table 3. Results of the ITT-LOCF Analysis in the Sample of 43 Patients[a]

Scale	Baseline Score, Mean ± SD	Score at 10 Months, Mean ± SD	Within-Subjects Effect (Duration)	Between-Subjects Effect (Treatment)	Duration-by-Treatment Interaction
CGI-S			$F=4.89$; $P=.039$ $\eta^2=0.2$	$F=7.45$; $P=.011$ $\eta^2=0.26$	$F=3.61$; $P=.063$ $\eta^2=0.17$
IPT-BPD-R	4.12 ± 0.86	3.29 ± 1.02			
WL/CM	4.27 ± 0.91	4.21 ± 0.79			
BIS-11			$F=8.37$; $P=.001$ $\eta^2=0.55$	$F=4.98$; $P=.033$ $\eta^2=0.2$	$F=4.76$; $P=.04$ $\eta^2=0.19$
IPT-BPD-R	80.74 ± 9.80	66.41 ± 13.22			
WL/CM	81.39 ± 7.31	78.57 ± 6.82			
BPDSI			$F=8.19$; $P=.001$ $\eta^2=0.53$	$F=7.68$; $P=.009$ $\eta^2=0.27$	$F=7.51$; $P=.01$ $\eta^2=0.26$
IPT-BPD-R	49.03 ± 6.34	37.31 ± 8.12			
WL/CM	47.78 ± 6.85	45.62 ± 6.62			
SOFAS			$F=5.15$; $P=.03$ $\eta^2=0.2$	$F=5.45$; $P=.022$ $\eta^2=0.22$	$F=2.68$; $P=.11$ $\eta^2=0.12$
IPT-BPD-R	57.48 ± 7.21	66.94 ± 8.32			
WL/CM	56.21 ± 9.02	56.60 ± 8.61			

[a]ANOVA for repeated measures was calculated to compare changes in scores on clinical rating scales in the 2 groups after treatment.

Abbreviations: ANOVA = analysis of variance, BIS-11 = Barratt Impulsiveness Scale–version 11, BPDSI = Borderline Personality Disorder Severity Index, CGI-S = Clinical Global Impressions–Severity of Illness scale, IPT-BPD-R = interpersonal psychotherapy adapted to borderline personality disorder–revised, ITT-LOCF = intention to treat–last observation carried forward, η^2 = eta squared (effect size), SOFAS = Social Occupational Functioning Assessment Scale, WL/CM = waiting list plus clinical management.

Treatment Outcome

Treatment outcome was assessed in the entire sample of 43 BPD patients using the intention to treat–last observation carried forward (ITT-LOCF) analysis. This included the 7 patients who had discontinued treatment. The results of the analysis of variance for repeated measures in BPD patients treated with IPT-BPD-R compared to BPD patients on the waiting list showed a significant improvement (within-subjects effect) with respect to the 4 clinical rating scales. Specifically, a significant decrease was observed for CGI-S ($P=.039$), BPDSI ($P=.001$), and BIS-11 ($P=.001$) scores, while SOFAS scores showed a significant increase ($P=.03$). Moreover, a significant between-subjects effect was found for scores on the 4 scales in favor of the IPT-BPD-R–treated group (CGI-S: $P=.011$; BPDSI: $P=.009$; BIS-11: $P=.033$; SOFAS: $P=.022$). The results are shown in detail in Table 3.

The patients included in this fMRI study were the same as those previously studied in a clinical response study.[51]

fMRI Results

We report the following results about T-contrasts of interest for keywords analyzed for the differences between the IPT-BPD-R group versus the group in waiting list.

Posttreatment versus pretreatment: unresolved life event condition versus neutral condition. The SVC-based analyses showed a significant decrease of activity in the rTPJ ($x=45$, $y=-51$, $z=36$) ($P=.043$) and in the rACC ($x=-4$, $y=37$, $z=8$) ($P=.021$) (Figure 1 and Table 4).

In addition, we analyzed the correlation between the change in activity of the rTPJ and rACC and the decrease in BPDSI total score for the contrast between unresolved condition and neutral condition in each group. In the IPT-BPD-R group, the change in activity of the 2 regions was significantly correlated with the decrease in BPDSI total score (rTPJ: $\rho=0.38$, $P=.022$; rACC: $\rho=0.41$, $P=.016$). No brain region showed a significant correlation with BPDSI total score in the WL/CM group.

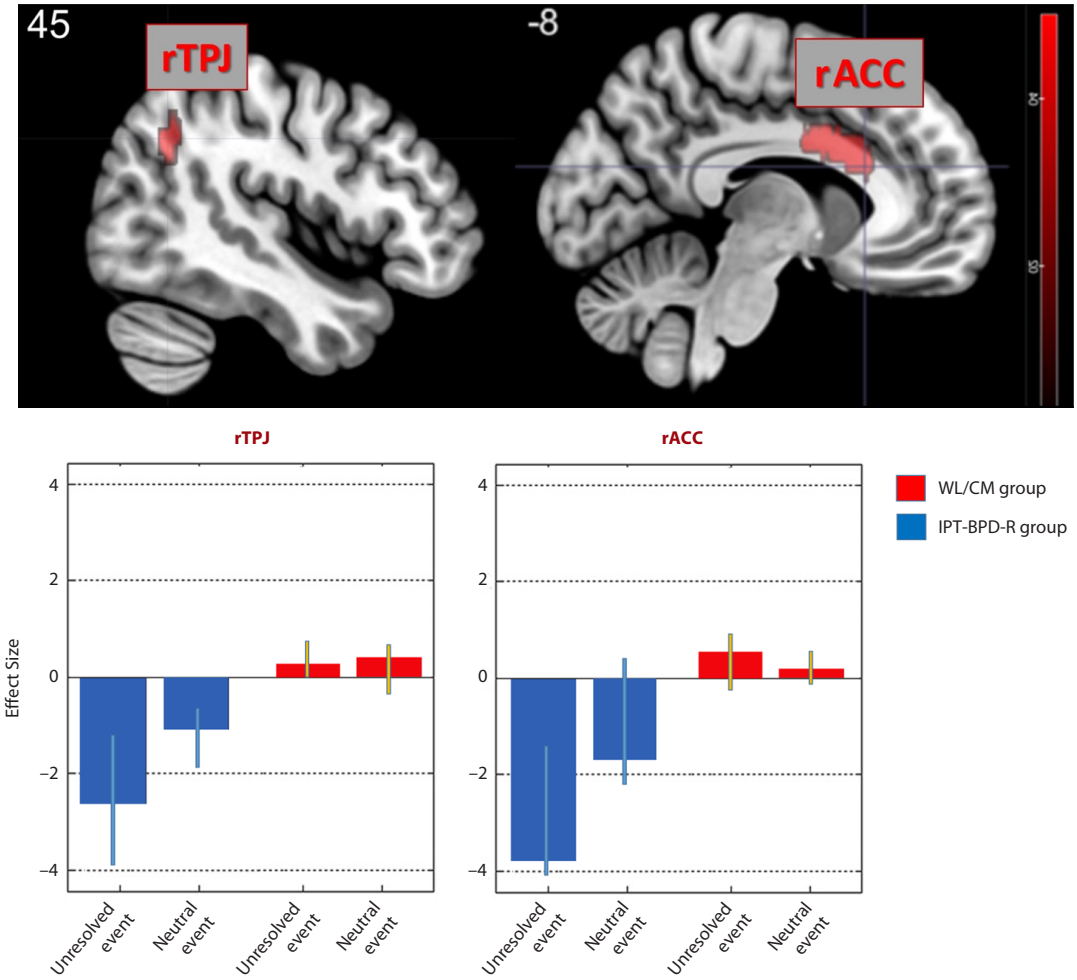
Posttreatment versus pretreatment: resolved life event condition versus neutral condition. Comparison between the IPT-BPD-R group and the WL/CM group for posttreatment fMRI run versus pretreatment fMRI run for the contrast-resolved condition versus neutral condition did not show any significant difference.

DISCUSSION

This neuroimaging study is the first designed to examine therapy-related changes in brain function in patients with BPD who have received BPD-adapted IPT compared with wait-listed patients. In light of the available evidence, it was hypothesized that patients with BPD receiving psychotherapy would exhibit modulation of neural activity patterns compared to untreated individuals. The hypothesis was confirmed by our results demonstrating significant differences in the activity of specific brain areas after IPT. Patients were exposed to unresolved and resolved life events as well as neutral stimuli during fMRI examination. Significant pre-post differences in brain function particularly affected the rACC and the rTPJ during exposure to the unresolved events obtained with AI compared to neutral stimuli. On the other hand, no significant changes in brain function were observed after IPT during exposure to the resolved events compared to neutral stimuli.

These results suggest that the efficacy of IPT-BPD-R on BPD symptoms may be underpinned by functional changes in brain areas involved in self-related processing, social cognition, and mentalization.[31,38,53–55] IPT-BPD-R may help increase awareness of one's emotions and distinguish one's

Figure 1. Comparison Between the IPT-BPD-R Group and the Waiting-List Group for Posttreatment fMRI Run Versus Pretreatment fMRI Run for the Contrast-Unresolved Condition Versus the Neutral Condition in the rTPJ and rACC[a]



[a]Parameter estimates for the single conditions unresolved event and neutral event for both groups are displayed. Statistical maps are displayed on a standard T1 template using the MRIcron software package[52] ($P < .05$, FWE-corrected). The bar graphs show the effect sizes for the 2 groups at the rTPJ and rACC.
Abbreviations: BPD = borderline personality disorder, fMRI = functional magnetic resonance imaging, FWE = family-wise error, IPT-BPD-R = interpersonal psychotherapy adapted to borderline personality disorder–revised, rACC = anterior cingulate cortex, rTPJ = right temporal parietal junction, WL/CM = waiting list plus clinical management.

Table 4. Contrasts of Interest for the IPT-BPD-R Group Versus the WL/CM Group for Posttreatment Versus Pretreatment[a]

	MNI Coordinates					
Anatomic Region[b]	*x*	*y*	*z*	*z*-Score	T Score	*P* Value
Right temporal parietal junction	45	−51	36	3.22	3.40	.043
Right anterior cingulate cortex	−4	37	8	4.13	4.56	.021

[a]Significant voxels are reported threshold of $P < .05$, corrected. Peak activity coordinates are reported in MNI space. All contrasts were computed using small volume correction (SVC) with a sphere of 10-mm radius and a statistical threshold of $P < .05$, FWE-corrected for multiple comparisons at the voxel level over small volumes of interest.
[b]Unresolved life event condition vs neutral condition.
Abbreviations: FWE = family-wise error, IPT-BPD-R = interpersonal psychotherapy adapted to borderline personality disorder–revised, MNI = Montreal Neurological Institute, WL/CM = waiting list plus clinical management.

own emotions from those of others, improve mobilization of cognitive and emotional resources needed to cope with interpersonal stress, modulate affective states in interpersonal contexts, reduce hypersensitivity to rejection, alleviate feelings of abandonment, and improve trust in others.[55]

Changes in brain function are associated with the clinical effects of psychotherapy. Therefore, the improvement in borderline symptom severity with IPT-BPD-R may also be observed in terms of modulation of brain activity between pre- and posttreatment.

Unfortunately, comparison with previous studies in this area is hampered by the fact that this study is the first to specifically examine the effect of IPT-BPD-R on brain activity. Our results can be compared only to studies that have examined brain activity before and after other psychotherapies for BPD, such as DBT and TFP.

The decrease in activity of the ACC after psychotherapy is consistent with the majority of available data obtained

in studies of DBT[29,31,32,35] and TFP.[34] There is a general consensus among studies that the ACC can be considered a target for the effects of psychotherapy, as it is involved in the mechanisms that allow individuals to orient not only in their own mental state, but also in the mental states of others.[56,57] The modulation of the ACC after IPT-BPD-R during the memory of unresolved life events may underlie the effects on affective states and impulsivity in patients treated with psychotherapy specific for BPD.

In contrast to ACC activity, there are no previous data from brain imaging studies on the effect of psychotherapy on TPJ activity. However, several previous studies have identified the TPJ as the major neural structure involved in processes of mentalization[58] and appraisal of emotional states in social situations.[59–62]

Our results showed that BPD patients treated with IPT-BPD-R showed a significant decrease in rTPJ activity when exposed to unresolved life events during fMRI examination. One possible explanation is that psychotherapy produces improvement in BPD symptoms, including impulsivity, with positive effects on self-perception, awareness, and social cognition. Specifically, BPD patients' belief that "others will reject them" is attenuated.[55] Improvements in interpersonal interactions and social inclusion enable patients to cope with unresolved life events using more appropriate strategies. These clinical and behavioral effects are consistent with modulation of brain activity in structures that play a key role in the theory of mind network.[63]

The greatest strength of this study is that it is the first evaluation of the effects of interpersonal psychotherapy for BPD (IPT-DBT-R) on patients' brain activity during an fMRI task.

The study suffers from some limitations. The first limitation is related to the exclusion of comorbid psychiatric disorders to obtain a sample with more homogeneous clinical characteristics and to avoid the effects of comorbidity on treatment response. The negative impact of this exclusion is that this sample is not fully representative of the clinical population of BPD patients, which is generally characterized by a high rate of psychiatric comorbidity. Another limitation relates to the fMRI task, which involves exposing subjects to unresolved and resolved life events identified with AI. BPD patients typically have an unstable self-concept and a tendency to change their opinion regarding significant life events whether they are or are not resolved during the time. To reduce the impact of this limitation, participants reviewed the summaries of life events immediately prior to the fMRI scans to confirm that each event had been correctly assigned to resolved or unresolved experiences. Finally, this study did not use a control group of non-patients, and a responder analysis to examine differences between patients who responded to psychotherapy and those who did not was not conducted.

Our preliminary results suggest that this specific psychotherapeutic intervention is effective in treating BPD symptoms and that the clinical effects are reflected in functional changes observed with neuroimaging techniques. The brain areas that showed a decrease in their activity are key structures of the theory of mind network, which are fundamental to the pathology of BPD. It would be of interest not only to replicate these findings, but also to conduct long-term studies to investigate possible delayed effects of IPT on the function of these areas.

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Supplementary Material

Article Title: How Interpersonal Psychotherapy Changes the Brain: A Study **of** fMRI in Borderline Personality Disorder

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List of Supplementary Material for the article

1. **Figure 1** Whole-brain contrast maps for *Post versus Pre: Unresolved life event condition versus neutral condition,* projected on a standard rendered SPM template brain

2. **Table 1** List of anatomical regions (p< 0.05 corrected). IPT-BPD-R group > waiting list condition group for Post > Pre

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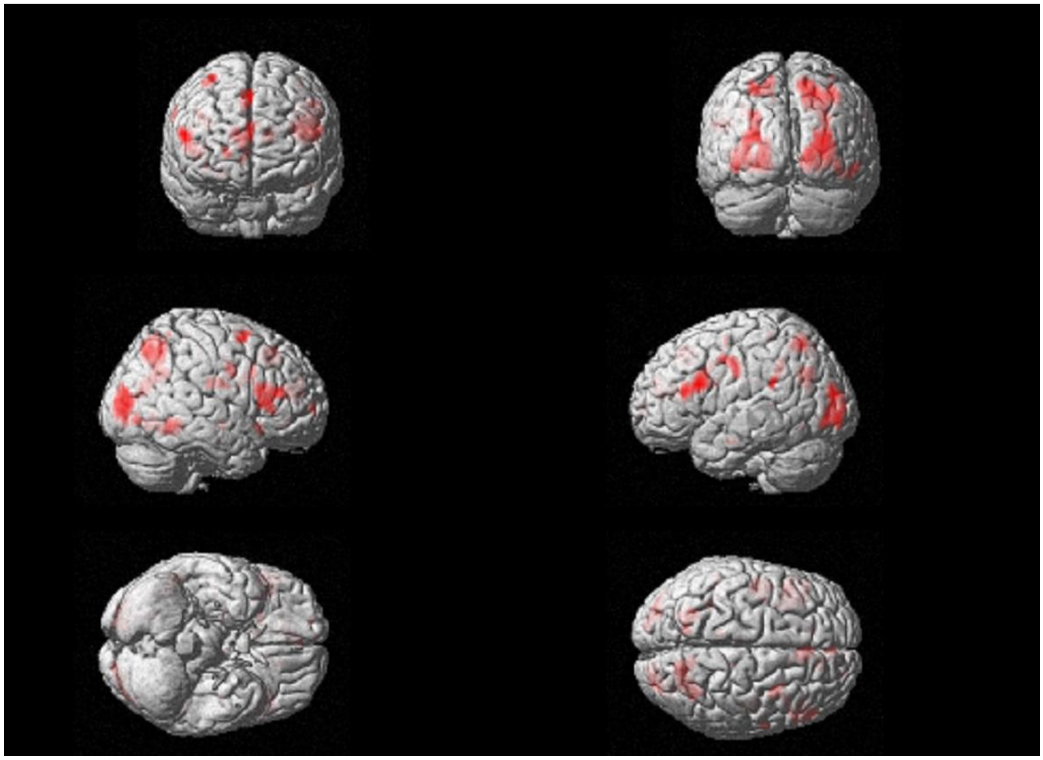
Supplementary Figure 1. Whole-brain contrast maps for *Post versus Pre: Unresolved life event condition versus neutral condition,* projected on a standard rendered SPM template brain.



Supplementary Table 1. List of anatomical regions (p< 0.05 corrected). IPT-BPD-R group > waiting list condition group for Post > Pre

	MNI Coordinates			Z-score	T-value	P-value
Anatomical Region	**X**	**Y**	**Z**			
Unresolved condition > neutral condition						
Right Temporal Parietal Junction	45	-52	34	4.22	3.30	.049
	39	-48	29	3.11	2.80	.052
Left Temporal Parietal Junction	-56	-42	23	2.88	2.35	.075
	-48	-39	32	2.14	2.33	.092
Right Anterior Cingulate Cortex	-4	37	8	4.13	4.56	.037
	-7	25	10	3.02	3.11	.051
	-5	41	12	2.59	2.62	.078
Left Dorsal Prefrontal Cortex	-29	45	8	2.65	2.40	.083
	-34	47	5	2.31	2.53	.079
Precuneus	0	-52	46	2.42	2.57	.081