# Change in Emotional and Theory of Mind Processing in Borderline Personality Disorder

## *A Pilot Study*

*Ueli Kramer, PhD,*†‡ Stéphane Kolly, MD,† Pauline Maillard, MPs,* Antonio Pascual-Leone, PhD,‡ Andrea C. Samson, PhD,§||¶ Ruth Schmitt, PhD,# Adriano Bernini, PhD,** Gilles Allenbach, MD,† Patrick Charbon, MD,† Yves de Roten, PhD,* Philippe Conus, MD,† Jean-Nicolas Despland, MD,* and Bogdan Draganski, MD**††*



**Abstract:** Changes in emotional processing (EP) and in theory of mind (TOM) are central across treatment approaches for patients with borderline personality disorder (BPD). Although the assessment of EP relies on the observation of a patient's self-criticism in a two-chair dialogue, an individual's TOM assessments is made based on responses to humorous stimuli based on false beliefs. For this pilot study, we assessed eight patients with BPD before and after a 3-month-long psychiatric treatment, using functional magnetic resonance imaging and behavioral tasks. We observed arousal increase within the session of the two-chair dialogue ($d = 0.36$), paralleled by arousal decrease between sessions ($d = 0.80$). We found treatment-associated trends for neural activity reduction in brain areas central for EP and TOM. Our exploratory findings using an integrative assessment procedure of changes in EP and TOM point toward evidence for treatment effects at the brain systems level related to behavioral modulation.

**Key Words:** Emotional processing, theory of mind, self-criticism, borderline personality disorder, fMRI

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Research in borderline personality disorder (BPD) has started to examine the neurobehavioral mechanisms related to the effects of treatment. Such research is central for an understanding why and how treatment for BPD works (Clarkin, 2014; Kazdin, 2009; Kramer, 2017, 2018). Schnell and Herpertz (2018) summarized central neurobehavioral factors in treatments for BPD. They pointed out that an increased integration in emotional and in sociocognitive processing is a central neuropsychotherapeutic mechanism of change in treatment of patients with BPD. Both factors—difficulties in emotional and sociocognitive processing—are central features associated with BPD (Carpenter and Trull, 2013; Choi-Kain and Gunderson, 2008; Goodman et al., 2004; Herpertz, 2011, 2013; Krause-Utz et al., 2014; Mier et al., 2013; New et al., 2007; Ruocco et al., 2013): change in these factors may be linked with the symptom relief in treatment.

There is evidence that the effects of treatments for BPD are associated with changes in emotional processing (EP). Schmitt et al. (2016) examined pre-post neural activity changes related to inpatient dialectical behavior therapy (DBT) program for patients with BPD ($n = 32$). They used the reappraisal paradigm (Schulze et al., 2011) assessing emotion regulation as a particular component of EP, in the functional magnetic resonance imaging (fMRI) environment. Results indicated that increased emotion regulation capacities facing negative visual stimuli were associated with treatment response, which in turn related to a specific increase in functional connectivity between the amygdala and the prefrontal cortex. It remains unclear whether the broader integration of EP, related to the individual patient's central self-critical concerns, changes in the treatment for BPD. In the present study, we define EP as an idiosyncratic process of transforming emotions related to self-criticism, from a self-contemptuous stance toward a more compassionate one toward the self (Kramer and Pascual-Leone, 2016; Kramer et al., 2015; Pascual-Leone, 2009).

Difficulties in sociocognitive processing have previously been linked with problems in BPD (Herpertz, 2013). The difficulty that patients present in the activity of inferring possible mental states of others—the individual's theory of mind (TOM; Saxe and Kanwisher, 2003; Sharp and Kalpakci, 2015)—is associated with several mental disorders, including BPD (Fonagy et al., 2015; Schnell and Herpertz, 2018). O'Neill et al. (2015) have studied the links between the patient's EP and TOM in patients with BPD ($n = 17$), using previously validated humorous visual stimuli (Samson et al., 2008). In this study, humorous cartoons were presented requiring perspective-taking skills of the perceiver to understand false beliefs of the protagonist presented in the cartoon (so-called TOM cartoons), in contrast to simpler forms of cartoons that involve visual ambiguity (so-called visual PUNs), as well as a nonhumorous control condition. The authors showed functional disconnection between neuronal regions associated with EP and regions associated with TOM (the left superior temporal lobe, right supramarginal and inferior parietal lobes, and the right middle cingulate; O'Neill et al., 2015). This pattern was not observed in healthy controls. So far, it remains unclear whether this lack of differentiation in the participant's TOM changes with treatment for BPD.

### An Integrated Approach to Mechanisms of Change

Both EP and TOM, as defined above, involve mechanisms that can be studied at both the psychological and neurobiological level. So far, studies in these domains, for example, EP across treatment for BPD, have taken into account one or the other perspective (*e.g.*, Berthoud et al., 2017; Goodman et al., 2014; Kramer et al., 2017a; Perez et al., 2016; Schmitt et al., 2016; Schnell and Herpertz, 2007). Despite significant advances,

*Institute of Psychotherapy, and †Service of General Psychiatry, Department of Psychiatry, Lausanne University Hospital (CHUV), University of Lausanne, Lausanne, Switzerland; ‡Department of Psychology, University of Windsor, Windsor, Ontario, Canada; §Swiss Center for Affective Sciences, University of Geneva, Geneva; || Swiss Distance Learning University, Brig; ¶Institut of Special Education, University of Fribourg, Switzerland; #Department of Psychiatry, University of Heidelberg, Heidelberg, Germany; **Laboratory for Research in Neuroimaging (LREN), Department of Clinical Neurosciences, Lausanne University Hospital (CHUV), University of Lausanne, Lausanne, Switzerland; and ††Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany.

Send reprint requests to PD Dr Ueli Kramer, Department of Psychiatry, Lausanne University Hospital (CHUV), University of Lausanne, Place Chauderon 18, CH-1003 Lausanne, Switzerland. E-mail: ueli.kramer@chuv.ch.

Ueli Kramer, Stéphane Kolly, Jean-Nicolas Despland, and Bogdan Draganski contributed equally to this work.



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we still lack deeper understanding about the link between the patient's idiographic experience observed in psychotherapy and the objective assessment of neural correlates of change.

A recent study has demonstrated that the use of individualized stimuli for patients with BPD shows stronger effects on emotional arousal related with sadness and other emotions, compared with standardized stimuli (Kuo et al., 2014). Consistently, individualized stimuli based on the patient's difficult memories were used in a recent fMRI study on patients with BPD who attempted suicide ($n$ = 60): patients with a suicide attempt showed decreased neural activations in the precuneus and the prefrontal cortex, associated with lack of cognitive distancing (*i.e.*, the patient being subjectively "overwhelmed" by emotions; Silvers, 2016); this effect was not found in patients without suicide attempt.

As such, we assume that symptom change in BPD is the result of a complex interplay between central process characteristics in the brain as measured from a neurobehavioral perspective (Kramer, 2017). The present pilot study uses a novel integrative methodology to assess two mechanisms of change in treatments of patients with BPD: a) change in EP and b) change in TOM, as they may be observed in a brief psychiatric treatment for BPD.

### Brief Integrative Treatment for BPD

To optimize interventions for as many patients with BPD as possible, Choi-Kain et al., 2016 and Gunderson (2016) (see also Chanen et al., 2016 and Paris, 2015) suggested a stepped care approach. As first-line treatment, a brief psychiatric intervention might be used implying minimal—"good enough"—training for therapists, to prepare the patient for a specialized—"stepped-up"—psychotherapeutic treatment. General psychiatric management was developed as comparison condition in the trial by McMain et al. (2009) and showed comparable outcomes with DBT. As a BPD-specific psychiatric intervention, it targets the core of its psychopathology: we assume that aspects of EP and TOM processing are expected to ameliorate under treatment. There is still insufficient understanding of the effectiveness and the initial mechanisms of change in such brief psychiatric treatments.

The present pilot study hypothesizes that a brief psychiatric treatment (10 sessions) is partly effective and produces initial changes in two main areas of psychobiological difficulties associated with BPD: EP and TOM. These changes should relate with initial symptom change. Specifically, we hypothesize that first a 10-session BPD-specific psychiatric treatment produces initial symptom reduction in BPD. Second, treatment presents with pre-post change in EP and TOM. Third, we assume that changes in EP and TOM are associated with treatment response.

## METHODS

### Participants

For the present pre-post pilot study, a total of $N$ = 8 female patients with BPD were included. They were assessed by trained clinicians using the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (*DSM-IV*) Axis II Personality Disorders (SCID-II) (First et al., 2004). They had a mean age of 23.1 (SD = 2.6) and presented with, on average, 6.4 *DSM-5* criteria of BPD. They were nonmedicated during the 10-session treatment and were all right handed. Patients with neurological disorders, bipolar disorder I, and schizophrenia were excluded from the study. All patients accepted that their data would be used for research, and the trial was approved by the competent institutional ethics board (125/15).

Four board-certified therapists treated all patients included in the current study with two patients per therapist. The therapists were three medical doctors and one psychologist with, on average, 4 years of experience in psychiatry. Each therapist treated two patients. They all had prior training in good psychiatric management (GPM), according to the guidelines described by Keuroghlian et al. (2016).

All patients underwent a brief intervention of 10 sessions over 3 months. The treatment followed a manual (Kolly S, Kramer U, Herrera F, Follonier G, Maksutaj R, Schopfer S, Marquet P, Preisig M [2010] Manuel du programme trouble de la personnalité: Investigation psychiatrique et psychodynamique. University of Lausanne [unpublished manuscript]), which was adapted from the GPM (Gunderson and Links, 2014). GPM has been shown in earlier studies to be an effective generalized treatment, both in the long-term treatment (McMain et al., 2009) and in the short-term treatment within a stepped-care approach (Kramer et al., 2014, 2017b). The treatment encompassed the establishment of a psychiatric diagnosis, the development of a treatment focus, and discussion of major symptoms and interpersonally relevant situations. Adherence to treatment was assessed using a questionnaire developed by Gunderson (2016), which was translated into French and given to the therapists after the delivery of the treatment (*i.e.*, therapist self-assessment once per patient). All patients received further treatment after the end of the 10-session initial treatment.

### Measures

Assessments took place before and after the brief treatment (Zanarini et al., 2010). Different, but matched, stimuli were used for both time points in the fMRI to avoid habituation effects (Koenigsberg, 2016). Patients were tested in the same point of the menstrual cycle. The first experimental task measuring EP used in this study encompasses: a) behavioral process assessment component and b) a neuroimaging assessment component, planned 1 week apart for both assessment points (Fig. 1). The humor task (measuring change in TOM) was an fMRI task only.

#### Emotional Processing

EP related to the patient's self-criticism is assessed using the self-criticism task (Doerig et al., 2014; Hooley et al., 2012). This task involves two main steps: a psychological assessment and a neurobiological assessment; they were 1 week apart.

(1) Conduct of a two-chair dialogue on self-criticism, an individualized emotion-arousing procedure (Greenberg, 2002; Kramer and Pascual-Leone, 2016; Whelton and Greenberg, 2005) with the aim of extracting 20 individualized self-critical words for each patient at each assessment point. The "two-chair" dialogue involved three substeps and three moments of manipulation checks (Fig. 1; Self-Assessment Manikin [SAM; Bradley and Lang, 1994] and State Self-Esteem Scale [SSES; Heatherton and Polivy, 1991]). For the first substep, the patient is invited to imagine a personal situation of failure of his or her life, as vividly as possible (without reporting verbally). The second substep involves the patient adopting the stance of the inner self-critical voice and expressing self-criticism (from a different chair, the "self-critical" one), addressed to the self, as imagined on the initial chair (Greenberg, 2002; Whelton and Greenberg, 2005). The third substep involves the patient (and back again on the initial chair) describing her current emotional reaction to the self-criticism (for a complete description of the two-chair dialogue used in research, see Kramer and Pascual-Leone, 2016). This assessment lasted for 30 minutes and was conducted pre- and posttherapy.

(2) fMRI during emotional reaction related to the individualized self-critical words ($n$ = 20 from step 1, substep 2 above), in comparison with sets of standardized negative emotional words ($n$ = 20; Kherif et al., 2011), standardized neutral words ($n$ = 20), and nonwords (symbols; $n$ = 20). The words were presented in the Cogent software developed by the Cogent 2000 team at the FIL and the ICN and Cogent Graphics developed by John Romaya at the LON at the Wellcome Trust Centre for Neuroimaging, University College London, UK. The participants received the following instruction: "Read the word and pay attention to what it evokes in you." Stimuli are presented for 2 seconds to the participant, then 1.5 seconds of assessment (one item from the SAM measuring arousal), and then 4 to 8 seconds of intertrial interval (jittered). This task was empirically

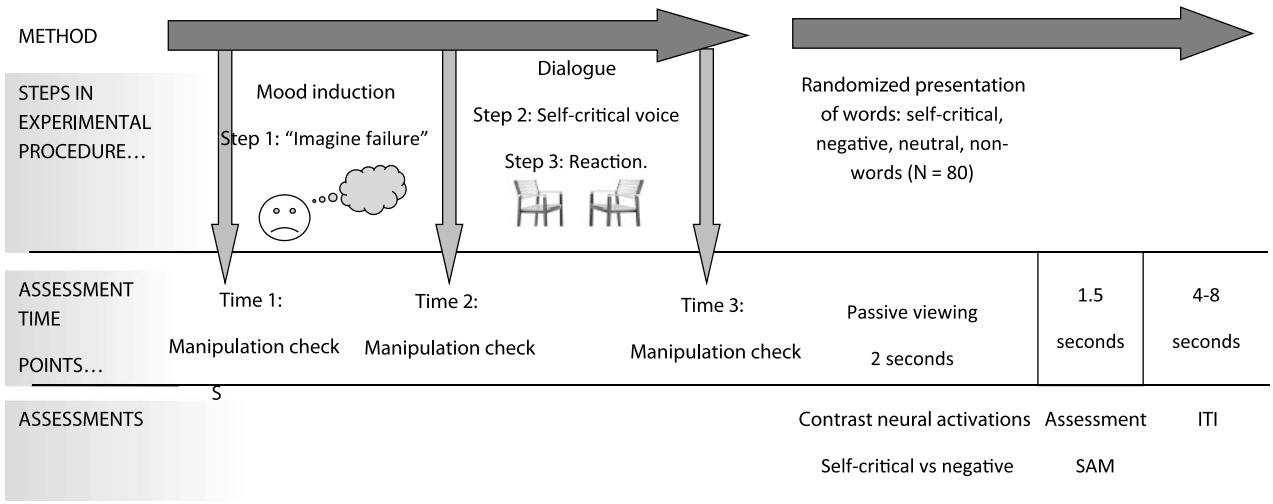


**FIGURE 1.** Behavioral assessment using the self-critical dialogue (modified from Kramer and Pascual-Leone, 2016). Note: "Manipulation checks" given at baseline (1), assessment points 2 and 3, and discharge (4); at all time points: visual analogue scale, SSES, SAM.

pretested. This pretest was successful: for $n = 5$ healthy controls, we showed for the individualized words higher subjective arousal levels (on the SAM: mean = 5.50, SD = 1.03) than for the standardized neutral words (on the SAM: mean = 1.04, SD = 0.03; standardized negative words on the SAM: mean = 4.28, SD = 1.90), along with differentiated functional activations (at $p < 0.05$ uncorrected). This task lasted for 14 minutes in the scanner and was conducted pre- and posttherapy.

### Theory of Mind

This fMRI task involves processing and understanding of humorous stimuli ("cartoons"; Samson et al., 2008, 2009); this task has previously been used in individuals with BPD (O'Neill et al., 2015). It involves three categories of stimuli: a) TOM—visual jokes requiring attributing false mental states to the protagonists presented in the cartoons (30 stimuli); b) PUN—visual puns, that is, cartoons that are based on visual similarities, not requiring attributing false mental states (30 stimuli); and c) a nonhumorous control condition with incongruent visual information (30 stimuli, in total $N = 90$). In this event-related design, each stimulus was presented for 6000 milliseconds, with variable stimulus onset delays (on average 10 seconds). Under the stimulus was printed "understood" (the joke) versus "not understood" (the joke), and the participants were instructed to "Look at the cartoon and decide to what extent you understand the joke (punch line) contained in it." This task lasted for 18 minutes in the scanner and was conducted pre- and posttherapy.

*Symptom change* is assessed using residual gains measured at discharge.

### Outcome Questionnaire–45.2

This self-report questionnaire encompasses 45 items aiming at assessing results yielded from treatment (Lambert et al., 2004), including a global score and three subscale scores: symptomatic level, interpersonal relationships, and social role. These items were assessed on a Likert-type scale ranging from 1 (never) to 4 (always); a total sum score and scores per subscale were computed. The scale has been translated and validated in French (Emond et al., 2004). This questionnaire was given at intake and at discharge of treatment. Cronbach's alpha for the current sample was $\alpha = 0.89$.

### Borderline Symptom List

The Borderline Symptom List (BSL-23) is a self-report questionnaire that assesses specific borderline symptomatology using 23 items, and it is a short version of the more extensive BSL-95 (Bohus et al., 2007), for which excellent psychometric properties were reported. Similar results were found for the short version (Bohus et al., 2009). The items are assessed using a Likert-type scale ranging from 0 (absent) to 4 (clearly present); an overall mean score is computed. The French translation (Page, Kramer, and Berthoud, unpublished data, 2010) was approved by the authors of the scale. Cronbach's alpha for the current sample was $\alpha = 0.90$.

### Self-Assessment Manikin

The SAM (Bradley and Lang, 1994) is a self-assessed questionnaire using a single item to measure the momentary level of arousal using a 9-point Likert scale, ranging from "not excited at all" (1) to "very excited" (9). This scale is widely used in emotion research and has proven its validity and reliability (*e.g.*, Bradley et al., 1992).

### State Self-Esteem Scale

The SSES (Heatherton and Polivy, 1991) is a self-report questionnaire encompassing 20 items. It assesses momentary self-esteem. A 5-point Likert scale was used. Validity of the scale, as well as its sensitivity to laboratory manipulations, was shown by Heatherton and Polivy (1991). An overall mean was computed. Cronbach's alpha for the current sample was $\alpha = 0.81$.

### Vividness of Visual Imagery

The Vividness of Visual Imagery (Marks, 1973) is a 16-item self-report questionnaire assessing the vividness of an imagery. A 5-point Likert scale, ranging from "not at all" (1) to "very vivid" (5), was used. The scale presented with a sufficient criterion-related and construct validity, as well as internal consistency (0.88) and test-retest reliability (0.74; McKenzie, 1995). An overall mean was used to have a manipulation check. Cronbach's alpha for this scale was $\alpha = 0.81$.

## Procedure

### Behavioral Data Analysis

For the behavioral outcome, we conducted intent-to-treat and completer analyses where appropriate, using paired sample *t*-tests (hypothesis 1). Raw scores for outcome and both potential mechanisms of change (EP and TOM) will be used (hypothesis 2). To link mechanisms of change with outcome (hypothesis 3), we use Spearman rank

**TABLE 1.** Manipulation Checks for All 16 Behavioral Assessments, Over Time ($n = 8$)

| | Time of Treatment Mean (SD) | | Within-Assessment Pre | | Within-Assessment Post | |
|---|---|---|---|---|---|---|
| | Pre | Post | *t* | ES | *t* | ES |
| Assessment 1 | | | | | | |
| SSES | 3.15 (0.64) | 2.97 (0.58) | | | | |
| SAM-arousal | 5.25 (2.66) | 3.75 (1.91) | | | | |
| Assessment 2 | | | | | | |
| SSES | 3.40 (0.86) | 3.01 (0.58) | 1.94 | 0.33 | 0.55 | 0.07 |
| SAM-arousal | 6.25 (2.87) | 4.00 (2.78) | 1.52 | 0.36 | 0.42 | 0.11 |
| Vividness | 4.06 (0.44) | 3.31 (0.80) | | | | |
| Assessment 3 | | | | | | |
| SSES | 3.03 (0.73) | 2.98 (0.80) | 0.33 | 0.17 | 0.08 | 0.01 |
| SAM-arousal | 6.00 (3.06) | 3.63 (2.88) | 1.00 | 0.26 | 0.16 | 0.04 |

Note. Assessment 1 (see Fig. 1), baseline; assessment 2, after imagination; assessment 3, end of two-chair dialogue. Within-assessment paired sample *t*-tests: comparing baseline with assessments 1 and 2, respectively.

correlations between the two change indexes (EP and TOM) and outcome. The statistical treatment package of SPSS.23 was used.

### MRI Data Acquisition

Our neuroimaging experiments followed the well-established methodology of blood oxygen level–dependent (BOLD) imaging followed by standard data processing and statistical analysis in the framework of SPM12.

The fMRI data were acquired on a Siemens Prisma 3 T with a 64-channel head coil using a two-dimensional echo planar imaging (EPI) sequence. The acquisition parameters were as follows: $3 \times 3 \times 3$ mm$^3$, echo time = 30 milliseconds, slice time of repetition = 66 milliseconds, 30 slices, flip angle = 90°. The structural MRI data consisted of T1-weighted magnetization prepared 180 degrees ratio frequency pulses and rapid gradient echo images (time of repetition = 2000 milliseconds; echo time = 920 milliseconds; $\alpha = 9°$; black-white = 250 Hz/pixel; readout in inferior-superior direction; field of view = 256 × 232 mm; 176 slices) at 1-mm resolution.

### MRI Data Preprocessing

All data preprocessing was performed using the freely available Statistical Parametric Mapping software (SPM12; Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/) running under MATLAB 7.13 (The MathWorks Inc, Natick, MA). EPI images were realigned to the subject's average image across runs and corrected for spatial distortions using the SPM fieldmap tools. The parameters of registration to standardized MNI space were calculated on the anatomical image and the default settings of the "unified segmentation" framework followed by the diffeomorphic registration algorithm DARTEL (Ashburner, 2007). The spatial registration parameters were then applied to the functional time series coregistered to the corresponding individual's anatomical scan. Before statistical analysis, we applied a spatial smoothing with a Gaussian kernel of 8-mm full width at half maximum.

### Subject-level fMRI Modeling

All statistical analyses were performed using the default settings in SPM12. The statistical analysis at subject-specific level was performed using the general linear model after convolving the event onsets with a canonical hemodynamic response function. Both time points were modeled as two separate sessions within the EP and the TOM design matrices.

For the EP task, we calculated at the subject level the interaction between WORDS (self-critical or standard negative words) and TIME (time point 1 versus time point 2) using abstract graphic symbols as baseline. For the TOM task, the subject-level differential t-contrast tested the interaction between TOM, PUN, and time point (the control stimuli were excluded from the data analysis).

#### *Group-Level Mass Univariate Analysis*

For both tasks, we used a one-sample *t*-test along with the OQ and SAM changes associated with treatment as regressors for the group-level analyses. The differential contrasts at the group level tested the positive and negative correlation between the interaction built at the subject-specific level and BOLD signal changes.

Given the low statistical power with 16 observations over two time points, we set liberal statistical significance levels at $p < 0.05$, uncorrected for multiple comparisons across the whole brain volume.

## RESULTS

### Behavioral Assessment

The manipulation checks of the self-critical task (*i.e.*, the two-chair dialogue) were performed in all 16 behavioral assessments (two per patient) and yielded satisfying results. There was an intratask increase in arousal ($d = 0.36$) and a decrease in state self-esteem ($d = 0.33$) at the second manipulation check (Assessment 2), compared with the first (baseline) manipulation check, whereas arousal and self-esteem levels at the third manipulation check were similar with regard to baseline ($d$'s between 0.17 and 0.26; Table 1). However, this pattern was not found for the behavioral posttreatment assessment where all $d$'s were smaller than 0.11. Therefore, we can assume that the two-chair dialogue increased the arousal level in the predicted manner in the initial assessment only (Kramer and Pascual-Leone, 2016; Whelton and Greenberg, 2005).

Manipulation checks related to arousal and state self-esteem were also taken pre- and post-fMRI assessment (Table 2). For pretherapy, arousal decreased over the time of the scanner session ($d = 0.60$), but self-esteem remained stable ($d = 0.21$). For posttherapy, arousal increased ($d = 0.36$), but self-esteem remained stable ($d = 0.22$).

Treatment integrity was satisfying to good, with a mean of 68% of correct responses on the therapist adherence scale for GPM (68/100 questions). No patient abandoned treatment nor stopped the neurobehavioral assessments. Therefore, all patients may be considered as completers in the present pilot trial.

### Treatment Outcome

Pre-post changes were tested for the $N = 8$ patients and yielded a consistent picture: all patients presented initial symptom reduction on

**TABLE 2.** Manipulation Checks for All 16 Neurofunctional Assessments, pre-post ($n = 8$)

| | Time of Treatment Mean (SD) | | Within-Assessment Pre | | Within-Assessment Post | |
|---|---|---|---|---|---|---|
| | Pre | Post | *t* | ES | *t* | ES |
| Assessment 1 | | | | | | |
| SSES | 3.01 (0.69) | 2.88 (0.76) | | | | |
| SAM-arousal | 5.38 (2.07) | 4.88 (2.10) | | | | |
| Assessment 2 | | | | | | |
| SSES | 2.86 (0.76) | 2.72 (0.72) | 2.21 | 0.21 | 1.80 | 0.22 |
| SAM-arousal | 4.00 (2.45) | 5.63 (2.07) | 1.94 | 0.60 | 0.75 | 0.36 |

Note. Assessment 1, before neurofunctional session; assessment 2, after neurofunctional session.

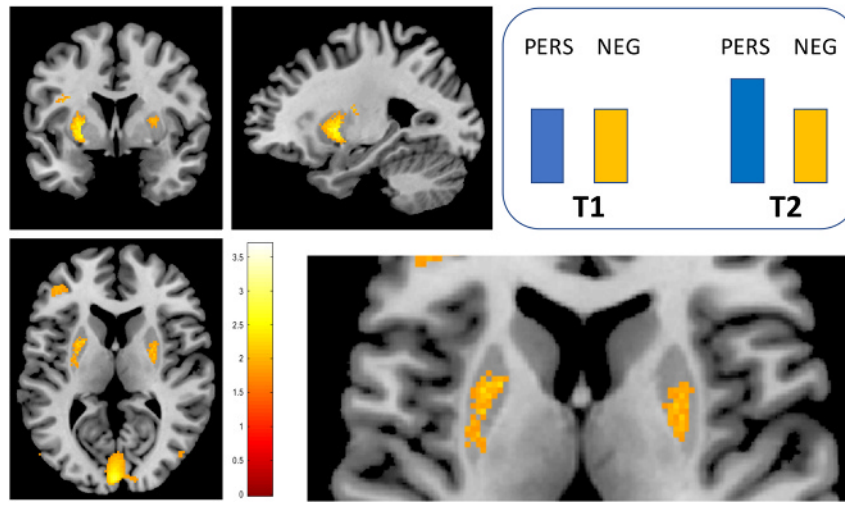


**FIGURE 2.** Statistical parametric maps of second-level interaction analysis between negative WORDS (individualized [PERS] or standardized [NEG]) and TIME (time point 1 [TP1] versus time point 2 [TP2]). *T*-values surviving $\alpha = 0.05$ uncorrected for multiple comparisons projected on a canonical anatomical image in Montreal Neurological Institute space.

all symptom measures over the 10-session treatment. Given the small sample size, it is not possible to know whether this reduction represents a significant change. Therefore, we report pre-post effect sizes in all cases. For the self-reported borderline symptoms (using the BSL-23), there was a trend in the reduction of symptoms ($t[7] = 1.94$, $p = 0.09$, $d = 0.51$). For the general problem and distress (using the Outcome Questionnaire–45.2 [OQ-45]), a small, but nonsignificant decrease was found ($t[7] = 1.87$, $p = 0.10$, $d = 0.42$).

## Changes in Emotional Arousal and Self-Esteem Over the Course of Treatment

When comparing peak arousal and problems in self-esteem (at assessment 2 in the behavioral component) between pretherapy and posttreatment, we found the following picture: arousal decreased after the imagination of the personal failure at posttreatment, compared with pretreatment, with a large effect size, but nonsignificance in the statistical comparison ($t[7] = 1.43$, $p = 0.19$, $d = 0.80$), along with a trend increase in state self-esteem, with a medium effect size ($t[7] = 2.18$, $p = 0.06$, $d = 0.53$). Although the tests were not statistically significant, the effect sizes ranged in the medium to large range for emotional change over the course of treatment and may therefore be interpreted with caution.

## fMRI Assessments

In the EP task, we observed a greater amount of neural activity change over time associated with the individualized self-critical words compared with standardized negative words in the associative putamen

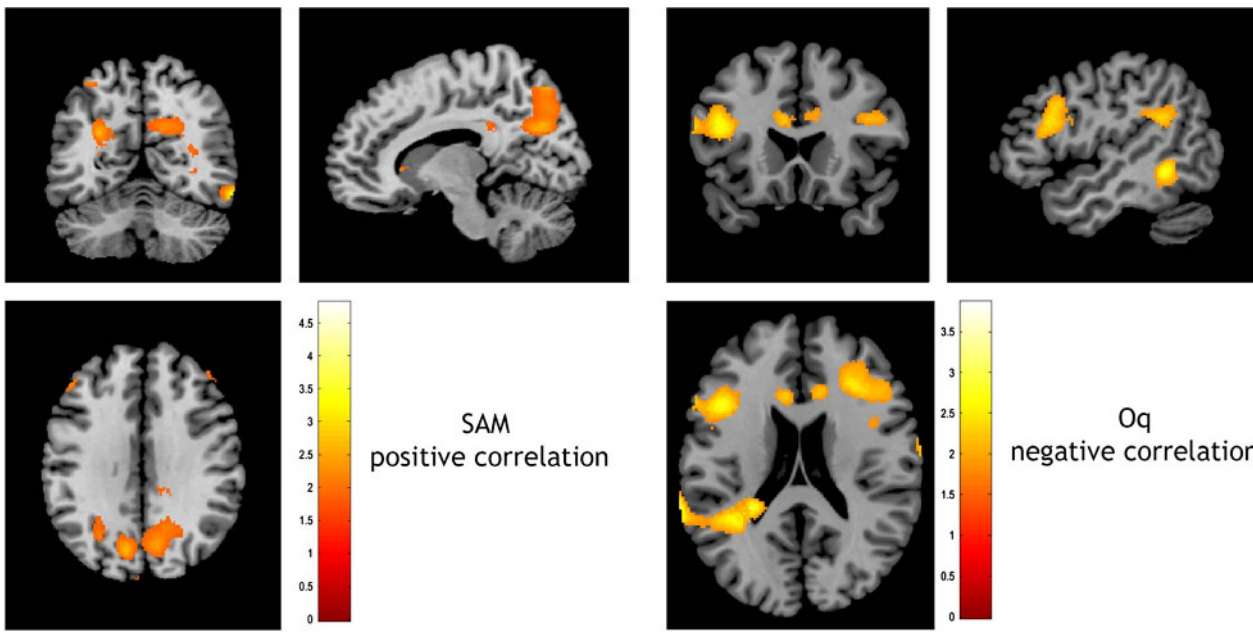


**FIGURE 3.** Statistical parametric maps of second-level correlation between clinical metrics (SAM and OQ) negative WORDS (individualized [PERS] or standardized [NEG]) and TIME (time point 1 [TP1] versus time point 2 [TP2]) interaction. *T*-values surviving $\alpha = 0.05$ uncorrected for multiple comparisons projected on a canonical anatomical image in Montreal Neurological Institute space.

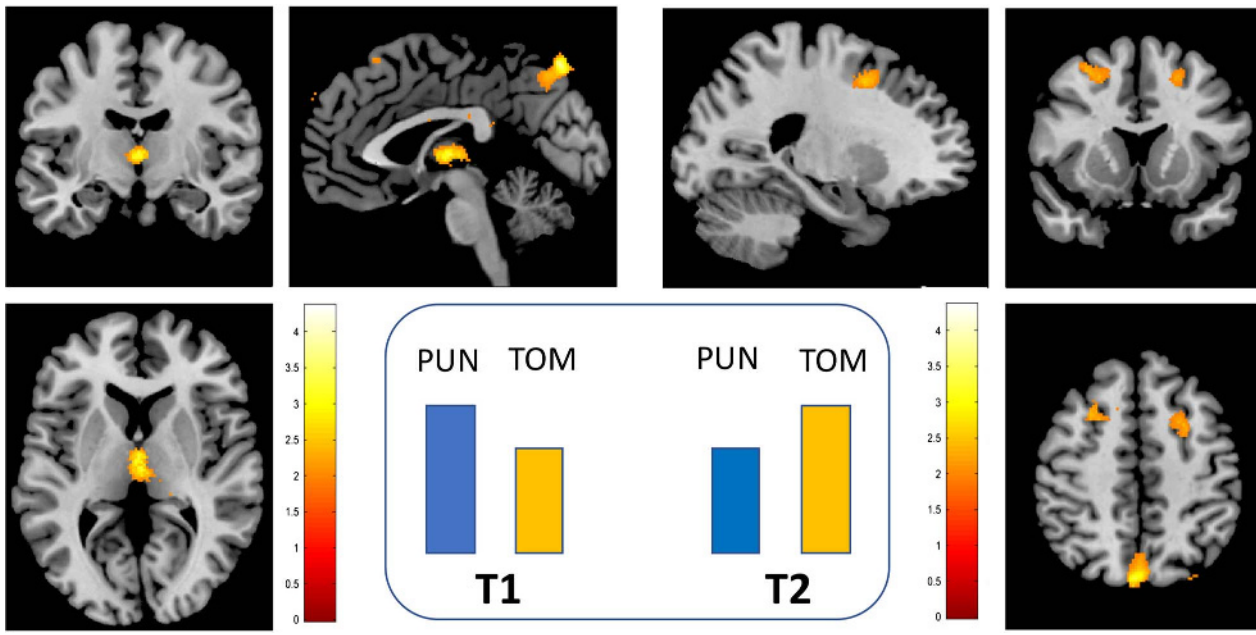


**FIGURE 4.** Statistical parametric maps of second-level interaction analysis between jokes requiring TOM, visual puns [PUN] and TIME (time point 1 versus time point 2). *T*-values surviving $\alpha = 0.05$ uncorrected for multiple comparisons projected on a canonical anatomical image in Montreal Neurological Institute space.

bilaterally, the left temporoparietal junction, and the left middle frontal gyrus (Fig. 2). There was a negative correlation between the neural activity changes and the OQ change over time in the inferior frontal gyrus bilaterally, the left temporoparietal junction, the left superior parietal lobule, and the left postcentral gyrus (Fig. 3). We demonstrated a positive correlation between SAM changes and the neural activity alterations over time involving the precuneus (Fig. 3).

In the TOM task, we observed changes in neural activity associated with a crossover interaction between TOM- and PUN-related responses implicating the mediodorsal nucleus of the thalamus, and the dorsolateral prefrontal cortex bilaterally where the trend was for TOM-associated increases and PUN-related decreases toward the end of the treatment (Fig. 4). The opposite pattern over time was related to neural activity changes affecting the orbitofrontal cortex, the anterior cingulate, and the ventral striatum bilaterally.

### Linking Neurobehavioral Mechanisms to Outcome

Using Spearman rank correlations, change in arousal in the behavioral task (assessment 2) was linked with change on the self-reported outcomes: BSL (rho = 0.28) and OQ-45 (rho = 0.37), whereas change in self-esteem in the behavioral task (assessment 2) was not linked with change on the self-reported outcomes BSL (rho = 0.05), but was linked with change on the OQ-45 (rho = 0.54). Interestingly, no significant correlation was found between the clinician-observed change in symptoms and change in arousal (rho = 0.01) and change in self-esteem (rho = 0.13).

When introducing treatment outcome (OQ change) and pre-post decrease in arousal (SAM change) as regressors in the statistical analyses on level 1 of the neural activity, OQ change was not significant, but SAM change was. For the EP, change in the peak arousal (SAM) from the behavioral assessment correlated significantly with the bilateral activation in the precuneus at posttreatment (Fig. 3). For the TOM task, pre-post change in the peak arousal (measured on the SAM) from the behavioral assessment correlated significantly with the activation in the left amygdala at posttreatment (Fig. 5).

## DISCUSSION

The present exploratory study examined a central question for psychotherapy research in BPD: Do emotional and sociocognitive functions change over the course of a brief treatment and are these changes related with symptom change? This study is the first to use an integrated measurement approach taking into account the individual's experience (Pascual-Leone et al., 2016a) to assess EP, in addition to TOM, in an fMRI environment.

This pilot study was able to confirm the feasibility of such integrated—neurobehavioral—assessments in psychotherapy research, confirm the pre-post effectiveness for symptom reduction of a brief treatment based on the GPM (Gunderson and Links, 2014) model and demonstrate acceptable treatment integrity. In addition, all manipulation checks performed on the behavioral tasks corresponded to the effects intended by the assessments (see also Kramer and Pascual-Leone, 2016).

This pilot study had four central preliminary findings, which should be tested in larger samples. First, between the beginning and the end of the brief treatment, the patients with BPD experienced a large subjective decrease in arousal when responding to their own idiographic contents. Pre-post treatment decrease in arousal was associated with symptom reduction, whereas the arousal peaked at both assessment points right after the imagery task in the behavioral assessment of EP (substep 1 of the self-criticism task). This result is consistent with an earlier study using a similar assessment procedure (*i.e.*, a two-chair dialogue for emotion-focused therapy; Kramer and Pascual-Leone (2016). This pattern—within-assessment increase in arousal and between-assessments decrease in arousal—has already been observed in research on EP, using a repeated expressive writing paradigm for traumatic memories (Pascual-Leone et al., 2016b). Such a "zigzag" pattern might represent the natural productive oscillation of arousal when individuals work through their idiographic core issues. In fact, it seems that such fluctuations have been overlooked in designs focusing more on the cognitive contents of the tasks (Longe et al., 2010). Our process perspective on arousal has the potential to help describe the more central phenomenon of emotional change.

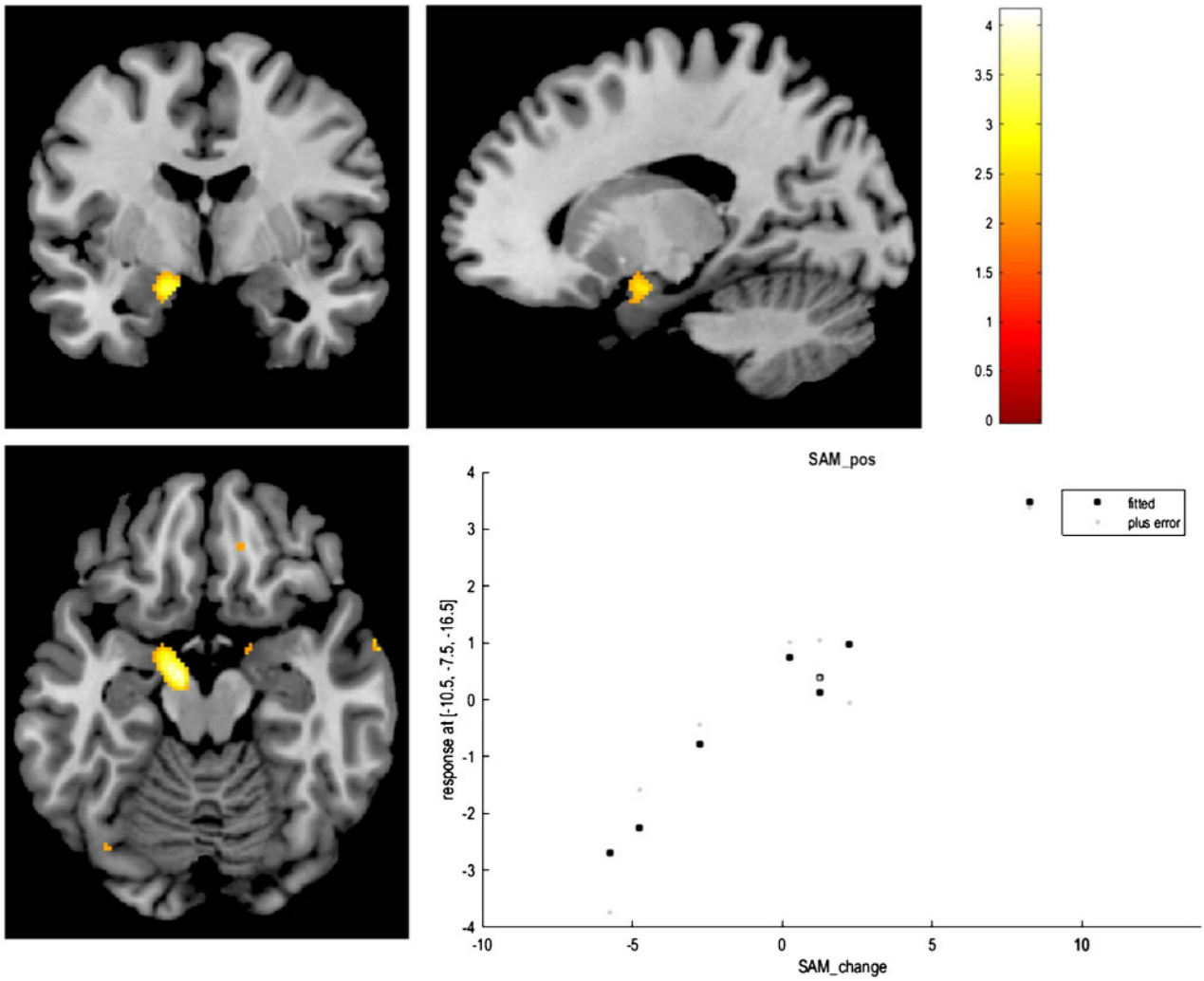


**FIGURE 5.** Statistical parametric maps of second-level correlation between clinical metrics (SAM) and interaction between jokes requiring TOM, visual puns [PUN], and TIME (time point 1 versus time point 2). *T*-values surviving $\alpha = 0.05$ uncorrected for multiple comparisons projected on a canonical anatomical image in Montreal Neurological Institute space.

Second, EP seems to change over the course of brief psychiatric treatment. When exposed to their own self-critical words, neuronal regions associated with the treatment of complex task of representation (*i.e.*, associative putamen; Rodriguez-Oroz et al., 2009) are increasingly recruited. It seems particularly interesting that the change in patient's subjective arousal is associated with the neuronal activity in the bilateral precuneus (Cavanna, and Trimble, 2006; Kjaer et al., 2002), when facing their own self-critical words. These structures are known for the treatment of reflective self-awareness and the development of consciousness. Self-awareness may have several sources (*i.e.*, cognitive, affective, sensorial); however, the design of the present study may suggest that patients most likely use an emotional self-awareness, integrating afferent information from the bodily felt sense related to the reaction to the self-critical words, toward an emergent representation directly from affective information (Kramer and Pascual-Leone, 2018).

Third, the present study showed change in the TOM network after a brief psychiatric treatment. This change was observed in the neuronal regions associated with treatment of complex information, resistance to change in beliefs (*i.e.*, the dorsolateral prefrontal cortex; Kaplan et al., 2016) and the TOM (*i.e.*, the orbitofrontal cortex, the nodal part of the mediodorsal thalamus; Mier et al., 2013; Mitchell, Chakraborty, 2013). Some of these regions are particularly affected in sociocognitive tasks in patients with BPD (Mier et al., 2013; Schmahl et al., 2014; Schnell and Herpertz, 2018). Most interestingly, change in the subjective arousal related to the behavioral assessment was linked with neural activity in the left amygdala, when the patients are exposed to TOM stimuli after treatment. Emotional relevance might actually be a central piece in the mind's processing of TOM stimuli, which may be reflected in this preliminary result. Alternatively, we may also hypothesize that the emotion regulation (recruiting structures like the amygdala) and the TOM networks are starting to reconnect, which would be consistent with the explanation exposed by O'Neill et al. (2015).

Fourth, change in arousal over the course of therapy may be linked with emotional and sociocognitive functioning. Relatedly, the change in arousal may explain directly the symptom change, but the neuronal activations remain unrelated with therapeutic outcome. Whereas the small sample size prevents us from drawing firm conclusions, we can hypothesize that the behavioral change seems to drive the outcome, and the behavioral changes may be underpinned with more subtle neuronal changes, which the present study has started to elucidate from an integrative assessment viewpoint.

Aiming to address methodological problems with an integrative approach that captures mechanisms of change in a theory-driven way,

we suggest taking into account the *individual's subjective experience* as anchor—substantiated in the form of *individualized* stimuli in the experiment—in the assessment of the mechanism of interest (Pascual-Leone et al., 2016a).

The present study has several limitations. Whereas the small sample size prevented us from conducting multiple testing, we adapted the statistical approach to the power (Button et al., 2013). Only a replication in a larger sample will help increase confidence in the results of the present pilot trial. In addition, we have not measured the actual emotional states in the assessment sessions, which may be a fruitful next step, in particular by analyzing the contemptuousness in the self-critical expressions (Kramer and Pascual-Leone, 2016; Whelton and Greenberg, 2005). Future studies using the present integrated neurobehavioral approach to assessment of mechanisms of change should aim at demonstrating statistical mediation of the treatment effect by the major patient pathways of change (EP and TOM) identified by the present pilot study. To control for confounds related with passing time, a control group will have to be included in a randomized design.

## CONCLUSION

We may cautiously put forward several clinical implications from integrative therapy perspective. The articulated approach to measurement, including the patient's subjective experience, enables us to suggest that the working through of self-critical aspects in BPD, using a two-chair dialogue, may be an adjunctive intervention of interest even if in the present study there was no therapeutic intent in the use of this assessment module. More globally, therapists may be advised to monitor microchanges in sociocognitive and EP in the therapeutic process (Schnell and Herpertz, 2018) and foster their transformation and differentiations within the context of a mechanism-based psychotherapy for BPD.

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## DISCLOSURE

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## REFERENCES

Ashburner J (2007) A fast diffeomorphic image registration algorithm. 39:95–113).

Berthoud L, Pascual-Leone A, Caspar F, Tissot H, Keller S, Rohde KB, de Roten Y, Despland J-N, Kramer U (2017) Leaving distress behind: A randomized controlled study on therapist responsiveness and client emotional processing in borderline personality disorder. *Psychiatry.* 80:139–154.

Bohus M, Kleindienst N, Limberger MF, Stieglitz RD, Domsalla M, Chapman AL, Steil R, Philipsen A, Wolf M (2009) The short version of the Borderline Symptom List (BSL-23): Development and initial data on psychometric properties. *Psychopathology.* 42:32–39.

Bohus M, Limberger MF, Frank U, Chapman A, Kühler T, Stieglitz RD (2007) Psychometric properties of the Borderline Symptom List (BSL). *Psychopathology.* 40: 126–132.

Bradley MM, Greenwald MK, Petry M, Lang PJ (1992) Remembering pictures: Pleasure and arousal in memory. *J Exp Psychol Learn Mem Cogn.* 18:379–390.

Bradley MM, Lang PJ (1994) Measuring emotion: The self-assessment Manikin and the semantic differential. *J Behav Ther Exp Psychiatry.* 25:49–59.

Button KS, Ioannidis JP, Mokrysz C, Nosek BA, Flint J, Robinson ES, Munafo MR (2013) Power failure: Why small sample size undermines the reliability of neuroscience. *Nat Rev Neurosci*. 14:365–376.

Carpenter RW, Trull TJ (2013) Components of emotion dysregulation in borderline personality disorder: A review. *Curr Psychiatry Rep*. 15:335.

Cavanna AE, Trimble MR (2006) The precuneus: A review of its functional anatomy and behavioural correlates. *Brain*. 129:564–583.

Chanen AM, Berk M, Thompson K (2016) Integrating early intervention for borderline personality disorder and mood disorder. *Harv Rev Psychiatry.* 24:330–341.

Choi-Kain LW, Albert EB, Gunderson JG (2016) Evidence-based treatments for borderline personality disorder: Implementation, integration and stepped care. *Harv Rev Psychiatry.* 24:342–356.

Choi-Kain LW, Gunderson JG (2008) Mentalization: Ontogeny, assessment, and application in the treatment of borderline personality disorder. *Am J Psychiatry.* 165: 1127–1135.

Clarkin J (2014) Raising the bar in the empirical investigation of psychotherapy. *Am J Psychiatry.* 171:1027–1030.

Doerig N, Schlumpf Y, Spinelli S, Späti J, Brakowski J, Quednow BB, Seifritz E, Grosse Holtforth M (2014) Neural representation and clinically relevant moderators of individualised self-criticism in healthy subjects. *Soc Cogn Affect Neurosci*. 9: 1333–1340.

Emond C, Savard K, Lalande G, Boisvert N, Boutin M, Simard V (2004) Propriétés Psychométriques de la Mesure d'Impact (MI-45), version francophone du Outcome Questionnaire (OQ-45.2) [*Psychometric Characteristics of the OQ-45, French Version*]. Annual Conference of ACFAS. Montreal, Canada.

First MB, Spitzer RL, Williams JBW, Gibbons M (2004) *Structured Clinical Interview for DSM-IV (French translation by M. Cottraux and J. Cottraux)* New York: Biometrics Research Department.

Fonagy P, Luyten P, Bateman A (2015) Translation: Mentalizing as treatment target in borderline personality disorder. *Personal Disord*. 6:380–392.

Goodman M, Carpenter D, Tang CY, Goldstein KE, Avedon J, Fernandez N, Mascitelli KA, Blair NJ, New AS, Triebwasser J, Siever LJ, Hazlett EA (2014) Dialectical behavior therapy alters emotion regulation and amygdala activity in patients with borderline personality disorder. *J Psychiatr Res*. 57:108–116.

Goodman M, New A, Siever L (2004) Trauma, genes, and the neurobiology of personality disorders. *Ann N Y Acad Sci*. 1032:104–116.

Greenberg LS (2002) *Emotion-focused therapy: Coaching clients to work through their feelings*. Washington, DC: American Psychological Association.

Gunderson JG (2016) The emergence of a generalist model to meet public health needs for patients with borderline personality disorder. *Am J Psychiatry.* 173:452–458.

Gunderson JG, Links PS (2014) *Handbook of good psychiatric management for borderline personality disorder.* Washington, DC: American Psychiatric Publishing Inc.

Heatherton TF, Polivy J (1991) Development and validation of a scale for measuring state self-esteem. *J Pers Soc Psychol*. 60:895–910.

Herpertz SC (2011) Affektregulation und ihre neurobiologischen Grundlagen. In Dulz B, Herpertz SC, Kernberg OF, Sachsse U (Eds). *Handbuch der Borderline-Störungen*pp 75–85). Stuttgart: Schattauer.

Herpertz SC (2013) The social-cognitive basis of personality disorders: Commentary on the special issue. *J Pers Disord*. 27:113–124.

Hooley JM, Siegle G, Gruber SA (2012) Affective and neural reactivity to criticism in individuals high and low on perceived criticism. *PLoS One*. 7:e44412.

Kaplan JT, Gimbel SI, Harris S (2016) Neural correlates of maintaining one's political beliefs in the face of counterevidence. *Sci Rep*. 6:39589.

Kazdin AE (2009) Understanding how and why psychotherapy leads to change. *Psychother Res*. 19:418–428.

Keuroghlian AS, Palmer BA, Choi-Kain LW, Borba CP, Links PS, Gunderson JG (2016) The effect of attending good psychiatric management (GPM) workshops on attitudes toward patients with borderline personality disorder. *J Pers Disord*. 30:567–576.

Kherif F, Josse G, Price CJ (2011) Automatic top-down processing explains common left occipito-temporal responses to visual words and objects. *Cereb Cortex*. 21:103–114.

Kjaer TW, Nowak M, Lou HC (2002) Reflective self-awareness and conscious states: PET evidence for a common midline parietofrontal core. *Neuroimage*. 17: 1080–1086.

Koenigsberg H (2016) *Borderline personality disorder patients show amygdala and anterior insula sensitization upon delay re-exposure to previously habituated negative images*. Presentation at the North American Society for the Study of Personality Disorders (NASSPD) Conference. New York.

Kramer U (2017) Personality, personality disorders and the process of change. *Psychother Res*.

Kramer U (2018) Mechanisms of change in treatments of personality disorders: Introduction to the special section. *J Pers Disord*. 32:1–11.

Kramer U, Keller S, Caspar F, de Roten Y, Despland J-N, Kolly S (2017a) Early change in coping strategies in responsive treatments for borderline personality disorder. A mediation analysis. *J Consult Clin Psychol*. 85:530–535.

Kramer U, Kolly S, Berthoud L, Keller S, Preisig M, Caspar F, Berger T, de Roten Y, Marquet P, Despland J-N (2014) Effects of motive-oriented therapeutic relationship in a ten-session general psychiatric treatment of borderline personality disorder: A randomized controlled trial. *Psychother Psychosom*. 83:176–186.

Kramer U, Pascual-Leone A (2016) The role of anger in self-criticism: An experimental study on emotional processes. *Couns Psychol Q*. 29: DOI:10.1080/09515070.2015.1090395.

Kramer U, Pascual-Leone A (2018) Self-knowledge in personality disorders: An emotion-focused perspective. *J Pers Disord*. 32:329–350.

Kramer U, Pascual-Leone A, Despland J-N, de Roten Y (2015) One minute of grief: Emotional processing in short-term dynamic psychotherapy for adjustment disorder. *J Consult Clin Psychol*. 83:187–198.

Kramer U, Stulz N, Berthoud L, Caspar F, Marquet P, Kolly S, de Roten Y, Despland J-N (2017b) The shorter the better? A follow-up analysis of 10-session psychiatric treatment including the motive-oriented therapeutic relationship for borderline personality disorder. *Psychother Res*. 27:362–370.

Krause-Utz A, Veer IM, Rombouts SA, Bohus M, Schmahl C, Elzinga BM (2014) Amygdala and anterior cingulate resting-state functional connectivity in borderline personality disorder patients with a history of interpersonal trauma. *Psychol Med*. 44:2889–2901.

Kuo JR, Neacsiu AD, Fitzpatrick S, MacDonald DE (2014) A methodological examination of emotion inductions in borderline personality disorder: A comparison of standardized versus idiographic stimuli. *J Psychopathol Behav Assess*. 36:155–164.

Lambert MJ, Morton JJ, tfield D, Harmon C, Hamilton S, Reid RC, Shimokowa K, Christoperson C, Burlingame GM (2004) *Administration and Scoring Manual for the Outcome Questionnaire–45*. Orem, UT: American Professional Credentialing Services.

Longe O, Maratos FA, Gilbert P, Evans G, Volker F, Rockliff H, Rippon G (2010) Having a word with yourself: Neural correlates of self-criticism and self-reassurance. *Neuroimage*. 49:1849–1856.

Marks DF (1973) Visual imagery differences in the recall of pictures. *Br J Psychol*. 64:17–24.

McKenzie SJ (1995) The VVIQ as a psychometric test of individual differences in a visual imagery vividness: A critical quantitative review and plea for direction. *J Men Imagery*. 19:1–106.

McMain SF, Links PS, Gnam WH, Guimond T, Cardish RJ, Korman L, Streiner DL (2009) A randomized trial of dialectical behavior therapy versus general psychiatric management for borderline personality disorder. *Am J Psychiatry*. 166:1365–1374.

Mier D, Lis S, Esslinger C, Sauer C, Hagenhoff M, Ulferts J, Gallhofer B, Kirsch P (2013) Neuronal correlates of social cognition in borderline personality disorder. *Soc Cogn Affect Neurosci*. 8:531–537.

Mitchell AS, Chakraborty S (2013) What does the mediodorsal thalamus do? *Front Syst Neurosci*. 7:3700037.

New AS, Hazlett EA, Buchsbaum MS, Goodman M, Mitelman SA, Newmark R, Trisdorfer R, Haznedar MM, Koenigsberg HW, Flory J, Siever LJ (2007) Amygdala-prefrontal disconnection in borderline personality disorder. *Neuropsychopharmacology*. 32:1629–1640.

O'Neill A, D'Souza A, Samson AC, Carballedo A, Kerskens C, Frodl T (2015) Dysregulation between emotion and theory of mind networks in borderline personality disorder. *Psychiatry Res*. 231:25–32.

Paris J (2015) Stepped care and rehabilitation for patients recovering from borderline personality disorder. *J Clin Psychol*. 71:747–752.

Pascual-Leone A (2009) Dynamic emotional processing in experiential therapy: Two steps forward, one step back. *J Consult Clin Psychol*. 77:113–126.

Pascual-Leone A, Herpertz SC, Kramer U (2016a) Experimental designs and the "emotion-stimulus critique": Hidden problems and potential solutions in the study of emotion. *Psychopathology*. 49:60–68.

Pascual-Leone A, Yeryomenko N, Morrison OP, Arnold R, Kramer U (2016b) Does feeling bad, lead to feeling good? Arousal patterns during expressive writing. *Rev Gen Psychol*. 20:336–347.

Perez DL, Vago DR, Pan H, Root J, Tuescher O, Fuchs BH, Leung L, Epstein J, Cain NM, Clarkin JF, Lenzenweger MF, Kernberg OF, Levy KN, Silbersweig DA, Stern E (2016) Frontolimbic neural circuit changes in emotional processing and inhibitory control associated with clinical improvement following transference-focused psychotherapy in borderline personality disorder. *Psychiatry Clin Neurosci*. 70:51–61.

Rodriguez-Oroz MC, Jahanshahi M, Krack P, Litvan I, Macias R, Bezard E, Obeso JA (2009) Initial clinical manifestations of Parkinson's disease: Features and pathophysiological mechanisms. *Lancet Neurol*. 8:1128–1139.

Ruocco AC, Amirthavasagam S, Choi-Kain LW, McMain SF (2013) Neural correlates of negative emotionality in borderline personality disorder: An activation-likelihood-estimation meta-analysis. *Biol Psychiatry*. 73:153–160.

Samson AC, Hempelmann CF, Huber O, Zysset S (2009) Neural substrates of incongruity-resolution and nonsense humor. *Neuropsychologia*. 47:1023–1033.

Samson AC, Zysset S, Huber O (2008) Cognitive humor processing: Different logical mechanisms in non-verbal cartoons—An fMRI study. *Soc Neurosci*. 3:125–140.

Saxe R, Kanwisher N (2003) People thinking about thinking people. The role of the temporo-parietal junction in "theory of mind". *Neuroimage*. 19:1835–1842.

Schmahl C, Herpertz SC, Bertsch K, Ende G, Flor H, Kirsch P, Lis S, Meyer-Lindenberg A, Rietschel M, Schneider M, Spanagel R, Treede RD, Bohus M (2014) Mechanisms of disturbed emotion processing and social interaction in borderline personality disorder: State of knowledge and research agenda of the German Clinical Research Unit. *Borderline Personal Disord Emot Dysregul*. 1:12.

Schmitt R, Winter D, Niedtfeld I, Herpertz SC, Schmahl C (2016) Effects of psychotherapy on neuronal correlates of reappraisal in female patients with borderline personality disorder. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 1:548–557.

Schnell K, Herpertz SC (2007) Effects of dialectic-behavioral-therapy on the neural correlates of affective hyperarousal in borderline personality disorder. *J Psychiatr Res*. 41:837–847.

Schnell K, Herpertz SC (2018) Emotion regulation and social cognition as functional targets of mechanism-based psychotherapy in major depression with comorbid personality pathology. *J Pers Disord*. 32(suppl):12–35.

Schulze L, Domes G, Krüger A, Berger C, Fleischer M, Prehn K, Schmahl C, Grossmann A, Hauenstein K, Herpertz SC (2011) Neuronal correlates of cognitive reappraisal in borderline patients with affective instability. *Biol Psychiatry*. 69:564–573.

Sharp C, Kalpakci A (2015) Mentalization in borderline personality disorder: From bench to bedside. *Personal Disord*. 6:347–355.

Silvers J (2016) *Suicide attempters in BPD show differential prefrontal and parietal recruitment when reappraising aversive memories*. Presentation at the North American Society for the Study of Personality Disorders (NASSPD) Conference. New York.

Whelton WJ, Greenberg LS (2005) Emotion in self-criticism. *Personal Individ Differ*. 38:1583–1595.

Zanarini MC, Stanley B, Black DW, Markowitz JC, Goodman M, Pilkonis P, Lynch TR, Levy K, Fonagy P, Bohus M, Farrell J, Sanislow C (2010) Methodological considerations treatment trials for persons with personality disorder. *Ann Clin Psychiatry*. 22:75–83.