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Change in emotional and theory of mind processing in borderline personality disorder: A pilot study

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Running Head: NEUROBEHAVIORAL CHANGE IN BPD

Change in emotional and theory of mind processing in borderline personality disorder: A pilot study

ABSTRACT

Changes in emotion processing (EP) and in theory of mind (TOM) are central across treatment approaches for patients with borderline personality disorder (BPD). Whilst the assessment of EP relies on the observation patient's self-criticism in a two-chair dialogue, 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 three-month long psychiatric treatment, using functional magnetic resonance imaging (fMRI) and behavioral tasks. We observed arousal increase within 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 towards evidence for treatment effects at the brain systems level related to behavioral modulation.

Keywords: emotional processing; theory of mind; self-criticism; borderline personality disorder; fMRI

INTRODUCTION

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, 2018; Kramer, 2017). Schnell and Herpertz (2018) summarized central neurobehavioral factors in treatments for BPD. They pointed out that an increased integration in emotional and in socio-cognitive processing are central neuropsychotherapeutic mechanisms of change in treatments of patients with BPD. Both factors – difficulties in emotional and socio-cognitive processing – are central features associated with BPD (Carpenter & Trull, 2013; Choi-Kain & Gunderson, 2008; Goodman, New & Siever, 2004; Herpertz, 2011; 2013; Krause-Utz, Veer, Rombouts, Bohus, Schmahl, & Elzinga, 2014; Mier, Lis, Esslinger, Sauer, Hangeoff, Ulferts, Gallhofer & Kirsch, 2013; New, Hazlett, Buchsbaum, Goodman, Mitelman, Newmark et al., 2007; Ruocco, Amirthavasagam, Choi-Kain, & McMain, 2013): change on 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, Winter, Niedtfeld, Herpertz and Schmahl (2016) examined pre-post neural activity changes related with an inpatient dialectical-behavioral therapy (DBT) program for BPD patients ($n = 32$). They used the reappraisal paradigm (Schulze et al., 2011) assessing emotion regulation, as a particular component of EP, in the 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 pre-frontal cortex. It remains unclear whether the broader integration of EP, related to the individual patient’s central self-critical concerns, changes in 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 towards a more compassionate one towards the self (Pascual-Leone, 2009; Kramer & Pascual-Leone, 2016; Kramer, Pascual-Leone, Despland, & de Roten, 2015).

Difficulties in socio-cognitive 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 & Kanwisher, 2003; Sharp & Kalkpakci, 2015) – is associated with several mental disorders, including BPD (Fonagy, Luyten, & Bateman, 2015; Schnell & Herpertz, 2018). O'Neill et al. have studied the links between the patient's EP and TOM in patients with BPD (n = 17), using previously validated humorous visual stimuli (Samson, Zysset & Huber, 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 non-humorous 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 lacking 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, Pascual-Leone, Caspar, Tissot, Keller, Rohde et al., 2017; Goodman, Carpenter, Tang, Goldstein, Avedon, Fernandez et al., 2014; Kramer, Keller, Caspar, de Roten, Despland, & Kolly, 2017; Perez, Vago, Pan, Root, Tuescher, Fuchs et al., 2016, Schmitt et al., 2016; Schnell & Herpertz, 2007). Despite significant advances, 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 to standardized stimuli (Kuo, Neacsiu, Fitzpatrick, & MacDonald, 2014). Consistently, individualized stimuli based on the patient's difficult memories were used in a recent fMRI study on suicide-attempters with BPD (n = 60): patients with a suicide attempt showed decreased neural activations in the precuneus and the pre-frontal 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: (1) change in EP, (2) change in TOM, as they may be observed in a brief psychiatric treatment for BPD.

<u>Brief integrative treatment for borderline personality disorder</u>

In order to optimize interventions for as many patients with BPD as possible, Gunderson (2016) and Choi-Kain, Albert and Gunderson (2016; see also Chanen, Berk, and Thompson, 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, in order to prepare the patient for a specialized – “stepped-up” – psychotherapeutic treatment. General Psychiatric Management was developed as comparison condition in the trial by McMain, Links, Gnam, Guimond, Cardish, Korman and Streiner (2009) and showed comparable outcomes with Dialectical-Behavior Therapy. As a BPD-specific psychiatric intervention, it targets the core of its psychopathology: we assume that aspects of emotional processing (EP) and theory of mind (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, firstly, a 10-session BPD-specific psychiatric treatment produces initial symptom reduction in BPD. Secondly, treatment presents with pre-post change in EP and TOM. Thirdly, 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 Borderline Personality Disorder (BPD) were included. They were assessed by trained clinicians using the 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 non-medicated 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 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, Palmer, Choi-Kain, Borba, Links and Gunderson (2015).

All patients underwent a brief intervention of 10 sessions over 3 months. The treatment followed a manual (Kolly, Kramer, Herrera, Follonier, Maksutaj, Schopfer et al., 2010) which was adapted from the Good Psychiatric Management (GPM; Gunderson & Links, 2014). GPM has shown in earlier studies to be an effective generalist treatment, both for the long-term treatment (McMain, Links, Gnam, Guimond, Cardish, Korman et al., 2009) and in the short-term treatment within a stepped-care approach (Kramer, Kolly, Berthoud, Keller, Preisig, Caspar et al., 2014; Kramer, Stulz, Berthoud, Caspar, Marquet, Kolly et al., 2017). 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 (October 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, Stanley, Black, Markowitz, Goodman, Pilkonis et al., 2010). Different, but matched, stimuli were used for both time points in the fMRI, in order 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 (1) behavioral-process assessment component and (2) a neuroimaging assessment component, planned 1 week apart for both assessment points (see Figure 1). The humor task (measuring change in TOM) was a fMRI task only.

Emotional processing (EP). EP related to the patient's self-criticism is assessed using the self-criticism task (Doerig, Schlumpf, Spinelli, Späti, Brakowski, Quednow et al., 2013 and Hooley, Siegle, & Gruber, 2012). This task involves two main steps, a psychological assessment and neurobiological assessment; they were one week apart.

(1) Conduct of a two-chair dialogue on self-criticism, an individualized emotion-arousing procedure (Whelton & Greenberg, 2005; Greenberg, 2002; Kramer & Pascual-Leone, 2016) with the aim of extracting 20 individualized self-critical words for each patient at each assessment point. The "two-chair" dialogue involved three sub-steps and three moments of manipulation checks (see Figure 1; Self-Assessment Manikin; SAM; Bradley & Lang, 1994, and Self-Esteem; SSES; Heatherton & Polivy, 1991). For the first sub-step, the patient is invited to imagine a personal situation of failure of this life, as vividly as possible

(without reporting verbally). The second sub-step involves the patient adopting the stance of the inner self-critical voice and express self-criticism (from a different chair, the “self-critical” one), addressed to the self, as imagined on the initial chair (Whelton & Greenberg, 2005; Greenberg, 2002). The third sub-step involved for the patient (and back again on the initial chair) describes 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 30 minutes and was conducted pre- and post-therapy.

(2) fMRI during emotional reaction related to the individualized self-critical words ($n = 20$ from step 1, sub-step 2 above), in comparison with sets of standardized negative emotional words ($n = 20$; Kherif, Josse, & Price, 2011), standardized neutral words ($n = 20$) and non-words (symbols; $n = 20$). The words are 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, UCL, UK. The participants received the following instruction: “Read the word and pay attention to what it evokes in you.” Stimuli are presented during 2 seconds to the participant, then 1.5 seconds of assessment (one item from SAM measuring arousal), then 4-8 seconds of inter trial interval (ITI, jittered). This task was empirically pre-tested. This pre-test 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 $p < .05$ uncorrected). This task lasted 14 minutes in the scanner and was conducted pre-and post-therapy.

Theory of Mind (TOM). This fMRI task involves processing and understanding of humorous stimuli ("cartoons"; Samson, Zysset, & Huber, 2008; Samson, Hempelmann, Huber, & Zysset, 2009); this task has previously been used in individuals with BPD (O'Neill et al., 2015). It involves three categories of stimuli: (1) TOM: visual jokes requiring attributing false mental states to the protagonists presented in the cartoons (30 stimuli), (2) PUN: visual puns, i.e., cartoons that are based on visual similarities, not requiring attributing false mental states (30 stimuli) and (3) a non-humorous control condition with incongruent visual information (30 stimuli, in total $N = 90$). In this event-related design, each stimulus was presented for 6000 ms, with variable stimulus onset delays (on average 10 s). Under the stimulus was printed "understood" (the joke) vs "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 18 minutes in the scanner and was conducted pre- and post-therapy.

Symptom change is assessed using residual gains measured at discharge.

Outcome Questionnaire – 45.2 (OQ-45). This self-report questionnaire encompasses 45 items aiming at assessing results yielded from treatment (Lambert, Morton, Hatfield, Hamilton, Reid, Shimokowa, Christoperson, & Burlingame, 2004), including a global score and three sub-scale scores: symptomatic level, interpersonal relationships and social role. These items are assessed on a Likert-type scale ranging from 1 (never) to 4 (always); a total sum score and scores per sub-scale are computed. The scale has been translated and validated in French (Emond, Savard, Lalande, Boisvert, Boutin, & Simard, 2004). This questionnaire was given at intake and at discharge of treatment. Cronbach's alpha for the current sample was $\alpha = .89$.

Borderline Symptom List (BSL-23). This self-report questionnaire assesses specific borderline symptomatology using 23 items and it is a short version of the more extensive BSL-95 (Bohus, Limberger, Frank, Chapman, Kühler, & Stieglitz, 2007) for which excellent psychometric properties were reported. Similar results were found for the short version (Bohus, Kleindienst, Limberger, Stieglitz, Domsalla, Chapman, Steil, Philipsen, & Wolf, 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, & Berthoud, 2010) was approved by the authors of the scale. Cronbach's alpha for the current sample was $\alpha = .90$.

Self-Assessment Manikin (SAM). The SAM (Bradley & 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, Greenwald, Petry, & Lang, 1992).

State Self-Esteem Scale (SSES). The SSES (Heatherton & 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 alpha for the current sample was .81.

Vividness of Visual Imagery (VVIQ). The VVIQ (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 (.88) and test-retest reliability (.74; McKelvie, 1995). An overall mean was used, in order to have a manipulation check. Cronbach alpha for this scale was .81.

Procedure

Behavioral data analysis. For the behavioral outcome, we conduct 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). In order to link mechanisms of change with outcome (hypothesis 3), we use Spearman rank correlations between the two change indexes (EP and TOM) and outcome. Statistical treatment package of SPSS.23 is used.

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

The fMRI data was acquired on a Siemens Prisma 3T with a 64-channel head coil using a 2D EPI sequence. The acquisition parameters were as follows: 3 x 3 x 3 mm3: TE =30 ms, slice TR = 66 ms, 30 slices, flip angle = 90°. The structural MRI data consisted of T1-weighted MPRAGE images (TR = 2000 ms; TI = 920 ms; α = 9°; BW = 250 Hz / pixel; readout in inferior-superior direction; FoV = 256 x 232 mm; 176 slices) at 1 mm resolution.

MRI data pre-processing. All data pre-processing 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, Massachusetts, United States). EPI images were realigned to the subject's average image across runs, corrected for spatial distortions using the SPM fieldmap tools (Hutton, 2002). 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 and Friston, 2005; Ashburner, 2007). The spatial registration parameters were then applied to the functional time-series co-registered to the corresponding individual's anatomical scan. Prior to statistical analysis, we applied a spatial smoothing with a Gaussian kernel of 8 mm full-width-at-half-maximum.

Subject-level fMRI modelling. 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 (GLM) after convolving the event onsets with a canonical hemodynamic response function (Friston et al., 1994, 1995; Worsley and Friston, 1995). 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 vs 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 intra-task 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; see Table 1). However, this pattern was not found for the behavioral post-treatment 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 & Pascual-Leone, 2016; Whelton & Greenberg, 2005).

Manipulation checks related to arousal and state self-esteem were also taken pre- and post-fMRI assessment (see Table 2). For pre-therapy, arousal decreased over the time of the scanner session (d = 0.60), but self-esteem remained stable (d = 0.21). For post-therapy, 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 Good Psychiatric Management (68/100 questions). No patient abandoned treatment, nor stopped the neuro-behavioral 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 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 t what the self-reported borderline symptoms (using the BSL-23), there was a trend in the reduction of symptoms ($t(7) = 1.94$; $p = .09$; $d = 0.51$). For the general problem and distress (using the OQ-45), a small, but non-significant decrease was found ($t(7) = 1.87$; $p = .10$; $d = 0.42$).

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 pre-therapy and post-treatment, we found the following picture: Arousal decreased after the imagination of the personal failure at post-treatment, compared to pre-treatment, with a large effect size, but non-significance in the statistical comparison ($t(7) = 1.43$, $p = .19$; $d = 0.80$), along with an trend increase in state self-esteem, with a medium effect size ($t(7) = 2.18$, $p = .06$; $d = 0.53$). Even though 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 greater amount of neural activity change over time associated with the individualized self-critical words compared to standardized negative words in the associative putamen bilaterally, the left temporo-parietal junction and the left middle frontal gyrus (see Figure 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 temporo-parietal junction, the left superior parietal lobule and the left postcentral gyrus (see Figure 3). We demonstrate a positive correlation between SAM changes and the neural activity alterations over time involving the precuneus (see Figure 3).

In the TOM task we observed changes in neural activity associated with a cross-over interaction between TOM and PUN-related responses implicating the medio-dorsal nucleus of the thalamus, and the dorsolateral prefrontal cortex bilaterally where the trend was for TOM-associated increases and PUN-related decreases towards the end of the treatment (see Figure 4). The opposite pattern over time was related to neural activity changes affecting the orbito-frontal 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 = .28) and on the OQ-45 (rho = .37), whereas change in self-esteem in the behavioral task (assessment 2) was not linked with change on the self-reported outcomes BSL (rho = .05), but was linked with change on the OQ-45 (rho = .54). Interestingly, no significant correlation was found between the clinician-observed change in symptoms and change in arousal (rho = .01) and change in self-esteem (rho = .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 post-treatment (see Figure 3). For the TOM task, pre-post change in the peak arousal (measured on the SAM) from the behavioral assessment correlated significant with the activation in the left amygdala at post-treatment (see Figure 5).

DISCUSSION

The present exploratory study examined a central question for psychotherapy research in borderline personality disorder: Do emotional and socio-cognitive 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., 2016), to assess emotional processing (EP), in addition to theory of mind (TOM), in a fMRI environment.

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

This pilot study had four central preliminary findings which should be tested in larger samples. Firstly, 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 emotional processing (sub-step 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 emotional processing, using a repeated expressive writing paradigm for traumatic memories (Pascual-Leone et al., 2016). 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., 2012). Our process perspective on arousal has the potential to help describe the more central phenomenon of emotional change.

Secondly, emotional processing 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, Jahanshani, Krack, Litvan, Macias, Bezard, & Obeso, 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, & Trimble, 2006; Kjaer, Nowak, Lou, 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, towards an emergent representation directly from affective information (Kramer & Pascual-Leone, 2018).

Thirdly, the present study showed change in the theory of mind 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, Gimbel, & Harris, 2016) and the theory of mind (i.e., the orbitofrontal cortex, the nodal part of the medio-dorsal thalamus; Mier, Lis, Esslinger, Sauer, Hagenhoff, Ulferts, Gallhofer, & Kirsch, 2013; Mitchell, Chakraborty, 2013; Singer et al., 2009). Some of these regions are particularly affected in socio-cognitive tasks in patients with BPD (Mier et al., 2013; Schmahl et al., 2014; Schnell & 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 theory of mind stimuli after treatment. Emotional relevance might actually be a central piece in the mind's processing of theory of mind 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 theory of mind networks are starting to re-connect, which would be consistent with the explanation exposed by O'Neill and colleagues (2015).

Fourthly, change in arousal over the course of therapy may be linked with emotional and socio-cognitive 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, Herpertz, & Kramer, 2016).

The present study has several limitations. Whereas the small sample size prevented us to conduct multiple testing, we adapted the statistical approach to the power (Button et al., 2013). Only a replication in a larger sample will help to increase confidence in the results of the present pilot trial. Also, 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 & Pascual-Leone, 2016; Whelton & 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, TOM) identified by the present pilot study. In order 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 (Pos & Greenberg, 2012) 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 micro-changes in socio-cognitive and emotional processing in the therapeutic process (Schnell & Herpertz, 2018) and foster their transformation and differentiations within the context of a mechanism-based psychotherapy for BPD.

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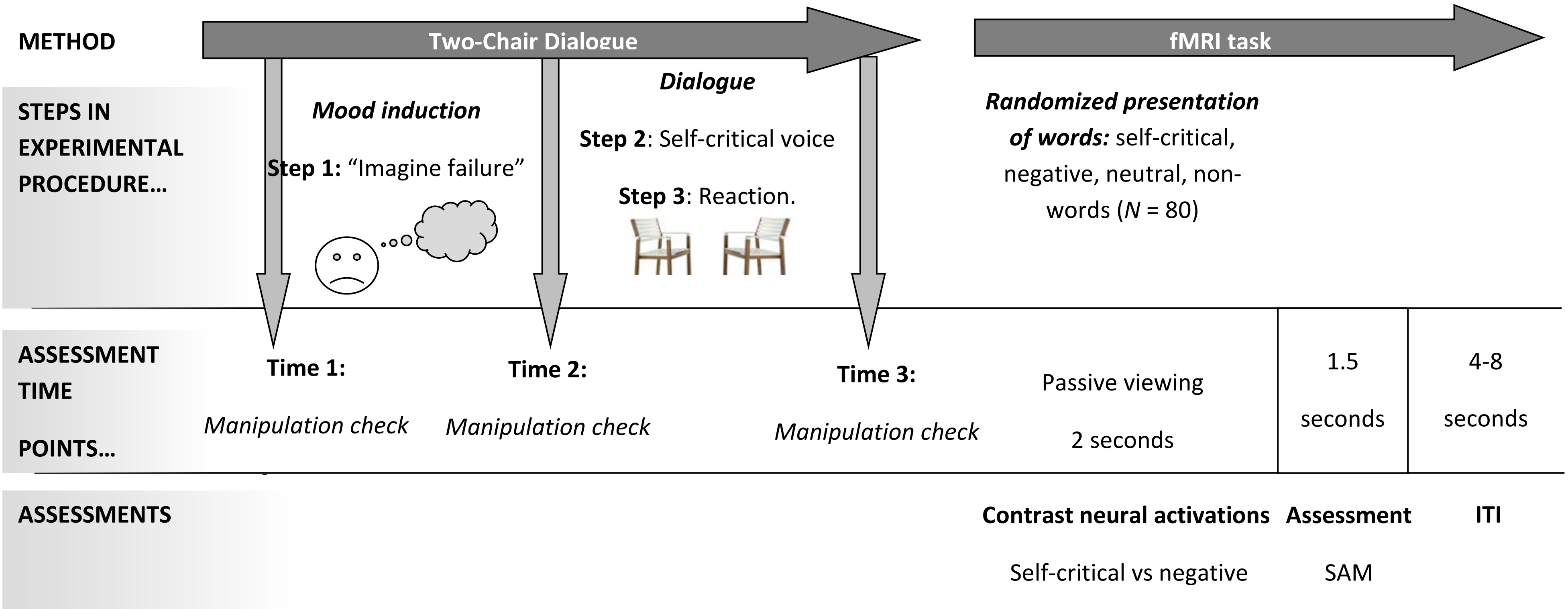
Figure 1

Behavioral assessment using the self-critical dialogue (modified from Kramer & 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; State Self-Esteem Scale; Self-Assessment Manikin

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

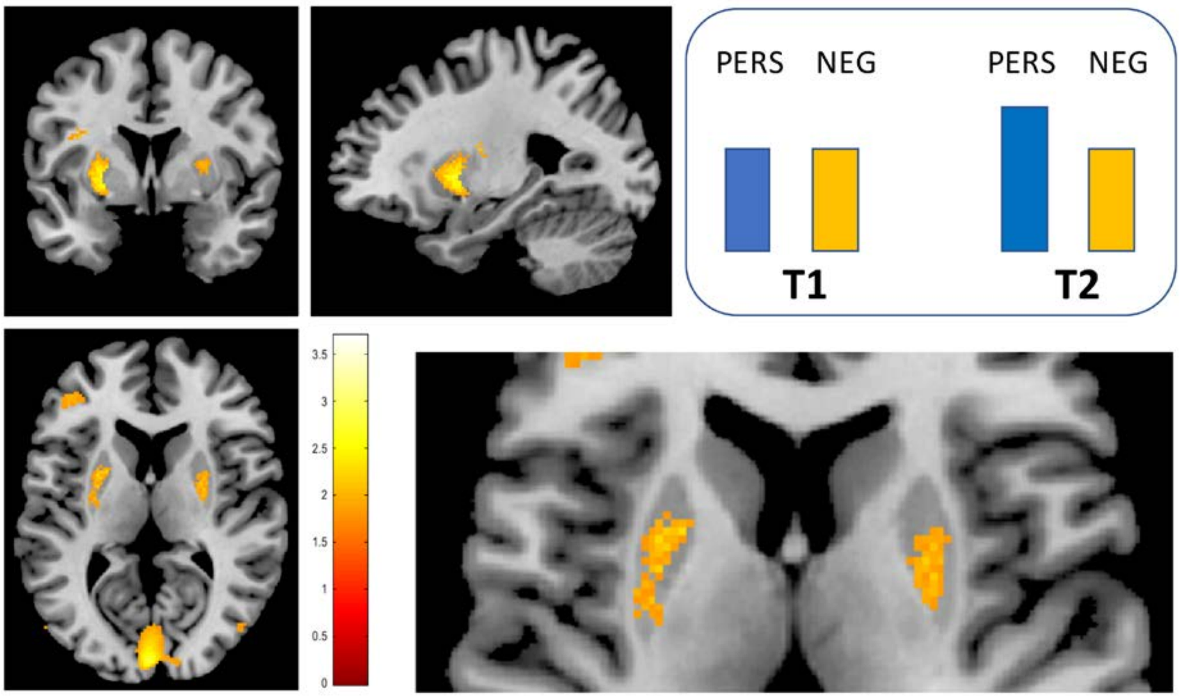


Figure 3. Statistical parametric maps of 2nd level correlation between clinical metrics (SAM and Oq) negative WORDS (individualized [PERS] or standardized [NEG]) and TIME (time point 1 – TP1 vs time point 2 – TP2) interaction. T-values surviving α = 0.05 uncorrected for multiple comparisons projected on a canonical anatomical image in Montreal Neurological Institute space.

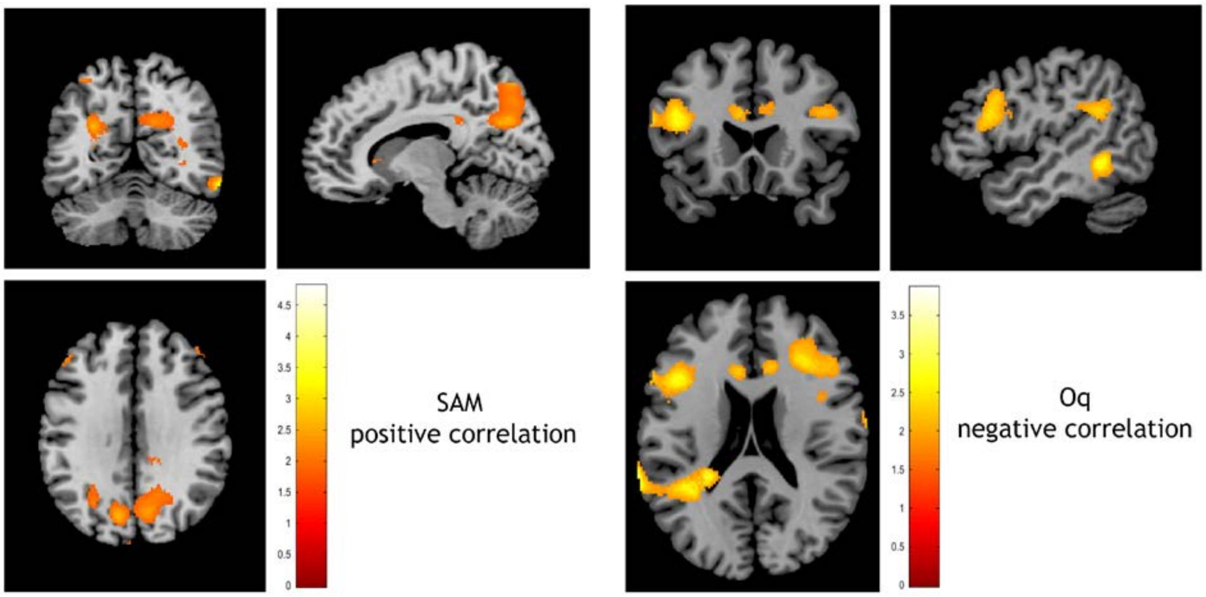


Figure 4. Statistical parametric maps of 2nd level interaction analysis between jokes requiring theory of mind [TOM], visual puns [PUN] and TIME (time point 1 vs time point 2). T-values surviving α = 0.05 uncorrected for multiple comparisons projected on a canonical anatomical image in Montreal Neurological Institute space.

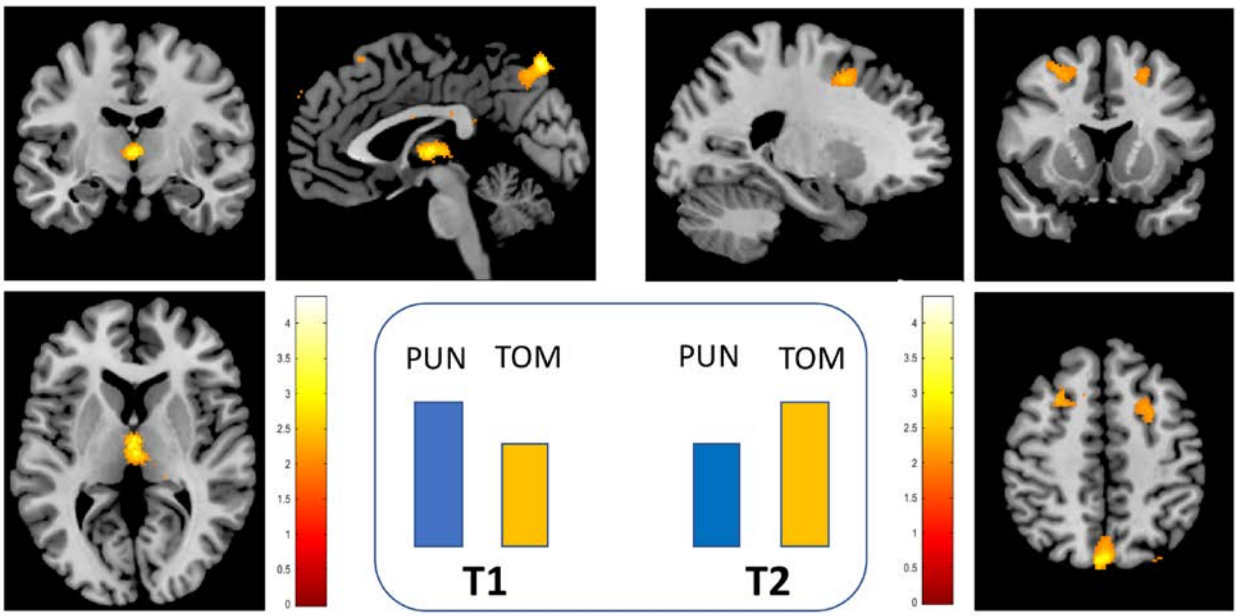


Figure 5. Statistical parametric maps of 2nd level correlation between clinical metrics (SAM) and interaction between jokes requiring theory of mind [TOM], visual puns [PUN] and TIME (time point 1 vs time point 2). T-values surviving α = 0.05 uncorrected for multiple comparisons projected on a canonical anatomical image in Montreal Neurological Institute space