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Regular Article

Frontolimbic neural circuit changes in emotional processing and inhibitory control associated with clinical improvement following transference-focused psychotherapy in borderline personality disorder

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Aims: Borderline personality disorder (BPD) is characterized by self-regulation deficits, including impulsivity and affective lability. Transference-focused psychotherapy (TFP) is an evidence-based treatment proven to reduce symptoms across multiple cognitive–emotional domains in BPD. This pilot study aimed to investigate neural activation associated with, and predictive of, clinical improvement in emotional and behavioral regulation in BPD following TFP.

Methods: BPD subjects ($n = 10$) were scanned pre- and post-TFP treatment using a within-subjects design. A disorder-specific emotional–linguistic *go/no-go* functional magnetic resonance imaging paradigm was used to probe the interaction between negative emotional processing and inhibitory control.

Results: Analyses demonstrated significant treatment-related effects with relative increased dorsal prefrontal (dorsal anterior cingulate, dorsolateral prefrontal, and frontopolar cortices) activation, and relative decreased ventrolateral prefrontal cortex and hippocampal activation following treatment. Clinical improvement in constraint correlated positively with relative increased left dorsal anterior cingulate cortex activation. Clinical improvement in affective lability correlated positively with left posterior-medial orbitofrontal cortex/ventral striatum activation, and negatively with right amygdala/parahippocampal activation. Post-treatment improvements in constraint were predicted by pre-treatment right dorsal anterior cingulate cortex hypoactivation, and pre-treatment left posterior-medial orbitofrontal cortex/ventral striatum hypoactivation predicted improvements in affective lability.

Conclusions: These preliminary findings demonstrate potential TFP-associated alterations in frontolimbic circuitry and begin to identify neural mechanisms associated with a psychodynamically oriented psychotherapy.

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BORDERLINE PERSONALITY DISORDER (BPD) is a mental illness characterized by self-regulation and interpersonal difficulties. This inability to self-regulate is manifested by rapid mood alterations and intense emotional/behavioral responses including impulsivity, aggression, and parasuicidal behaviors.[1,2] The mainstay of treatment is psychotherapy, while psychopharmacologic interventions have yielded mixed results. The prevalence of BPD is approximately 1.4%, and this condition utilizes disproportionally high rates of psychiatric and medical resources. Despite these statistics, both the neurobiology and treatment of BPD have received less investigative attention than other psychiatric conditions with similar morbidity. While neural substrates of symptom expression in BPD have been investigated, the mechanisms mediating symptom improvement following psychotherapy remain poorly characterized, and few studies have investigated neural changes associated with psychodynamic psychotherapy in any population.

Functional magnetic resonance imaging (fMRI) studies probing emotional processing in BPD have identified reduced top-down regulatory prefrontal cortex (PFC) and enhanced amygdala activity. Several studies in BPD demonstrated reduced anterior cingulate cortex (ACC), frontopolar cortex (FPC), and orbitofrontal cortex (OFC) activation in conjunction with increased amygdalar activation during negative emotional processing, suggesting decreased monitoring and regulation, as well as increased reactivity in the context of negative emotional stimuli. For example, BPD patients displayed reduced FPC, subgenual and rostral ACC activation in response to fearful facial emotions,[3] and failed dorsal and rostral ACC activation during a negatively valenced emotional word Stroop task.[4] Reduced OFC activation during script-driven imagery of self-injurious behavior[5] and attempted emotional re-appraisal[6] has also been reported. In addition to PFC dysfunction, increased amygdala activation during negatively valenced picture-viewing and fear-based tasks has been characterized in BPD.[3,7–10] Impaired amygdalar habituation[11] and aberrant ACC-amygdala, OFC-amygdala and subgenual ACC-dorsal ACC functional connectivity have also been demonstrated in BPD.[10,12] Studies of BPD have also characterized behavioral response-inhibition deficits during emotionally neutral tasks,[13,14] impairments in cognitive control associated with decreased constraint,[15] and enhanced recall of salient, negatively valenced emotional information.[16]

Our group previously designed an emotional linguistic *go/no-go* fMRI study to probe the clinically salient interaction of negative affective processing and inhibitory control in BPD and healthy subjects.[17,18] In healthy subjects, inhibitory control in the context of negative emotional processing selectively activated the posterior-medial OFC, dorsal ACC, dorsolateral prefrontal cortex (dlPFC), amygdala and hippocampus. When comparing BPD with healthy subjects, frontolimbic dysfunction was identified in the posterior-medial OFC and the dorsal and subgenual ACC. Specific deficits in self-reported restraint of impulsive behavior correlated with decreased posterior-medial OFC activation, while negative emotion correlated with increased extended amygdala/ventral striatum activation. Recently, use of a *go/no-go* task following anger induction identified reduced inferior frontal cortex activation in BPD compared to controls during motor inhibition.[19]

Transference-focused psychotherapy (TFP) is an evidence-based treatment for BPD, developed by Kernberg and colleagues, that relies on techniques of clarification, confrontation, and interpretation of affect-laden themes that emerge within the transference relationship.[20] In a randomized, blinded 1-year study, TFP reduced impulsivity, anger, irritability and suicidality, and demonstrated greater multi-symptom improvement compared to dialectical behavioral therapy and supportive psychotherapy.[21] Importantly, unlike the two comparison therapies, TFP significantly reduced impulsivity. This pilot study used a within-subjects design to investigate changes in frontolimbic neural activation during the interaction of inhibitory control and negative emotional processing in BPD patients treated with TFP. Longitudinal changes in neural activation and predictors of treatment response were investigated, emphasizing a

dimensional approach to study neural activity associated with symptom improvement in the clinically important domains of constraint, affective lability and aggression. We hypothesized decreased amygdalar activation and increased medial PFC activation associated with TFP-related clinical improvement, and also that baseline neural activation patterns in these regions would predict treatment response.

METHODS

Participants

Ten women with BPD (nine right-handed; mean age = 27.8 years, range = 23–32 years) were recruited from the New York Presbyterian Hospital/Weill Cornell Medical College–Westchester Division (Supplemental Table S1). BPD diagnoses were confirmed with the International Personality Disorder Examination[22] (criteria score range = 5–9, dimensional score range = 10–18; mean = 15.00, SD = 2.45). Other current diagnoses as measured by the Structured Clinical Interview for DSM-IV-TR Axis I Disorders included panic disorder ($n = 1$), social phobia ($n = 1$), specific phobia ($n = 1$), generalized anxiety disorder ($n = 3$), alcohol abuse ($n = 2$), and cannabis abuse ($n = 2$). Past diagnoses included major depressive disorder ($n = 6$), obsessive–compulsive disorder ($n = 1$), and alcohol dependence ($n = 2$). On the International Personality Disorder Examination, other categorical diagnoses included histrionic ($n = 3$), avoidant ($n = 1$), and narcissistic ($n = 2$) personality disorders.

Five patients reported psychotropic medication during study participation (Supplemental Table S1). Written informed consent was obtained and the protocol was approved by the institutional review board of New York Presbyterian Hospital/Weill Cornell Medical College. Subject recruitment, assessments, TFP treatments, and fMRI scan acquisitions were performed at New York Presbyterian Hospital/Weill Cornell Medical College. Data analyses and manuscript preparation were approved by the Partners Human Research Committee.

Following initial assessment and pre-treatment scanning, patients participated in TFP (average number of sessions attended = 76.60, SD = 8.28). TFP consisted of twice-weekly individual, 50-min sessions supervised by Otto F. Kernberg, MD and Frank Yeomans, MD, PhD. All therapists had advanced degrees in social work, psychology or psychiatry, with at least 2 years of prior experience treating BPD patients. Weekly supervision on all cases was provided for the five therapists. Ratings of adherence and competence were made by the supervisors on the TFP Adherence and Competence Rating Scale.[23] Interrater reliability between two raters was high (intraclass correlation coefficient [ICC] = 0.96). All participants received the Multidimensional Personality Questionnaire (MPQ),[24] the Affective Lability Scale (ALS)[25] and the Overt Aggression Scale-Modified (OAS-M)[26] prior to TFP and at follow-up scanning. The MPQ was used to relate the clinically relevant factor of constraint to functional neuroimaging results. A high level of constraint reflects tendencies to inhibit and restrain impulse expression. The ALS is a 54-item self-report instrument where subjects rate the tendency of their mood to shift between normal to affectively charged domains of anger, depression, elation and anxiety, as well as their tendency to shift between depression and elation and between depression and anxiety. OAS-M is a clinician-rated scale that characterizes aggressive behavior within the past week based on observation and self-report.

fMRI task

Participants underwent pre-treatment and post-treatment scanning (average scan interval = 12.1 months; range = 10–14 months) while they performed an emotional linguistic *go/no-go* task,[17] with verbal stimuli containing themes salient for BPD (Supplemental Figure S1). Participants were instructed to perform a right-index-finger button-press immediately after (silently) reading a word appearing in normal font (*go* trial) and to inhibit this response after reading a word in italicized font (*no-go* trial). Button-press responses and reaction times were recorded. Following scanning, participants performed word recognition and valence rating tasks.

fMRI data acquisition, image processing and analysis

Imaging data were acquired pre- and post-TFP with a GE SIGNA 3Tesla MRI scanner (GE Medical Systems, Milwaukee, WI, USA; Supplemental Methods). The fMRI imaging data processing procedures were performed using customized Statistical Parametric Mapping software, and a two-level voxel-wise linear random-effects model was utilized to examine the

effect sizes of the key Group/Condition contrasts in a three-way repeated-measures analysis of covariance (ANCOVA) setting (Supplemental Methods). Based on *a priori* hypotheses derived from our prior studies[18] as well as theoretical considerations,[17–19] regions of interest (ROI) were the bilateral posterior-medial OFC, ACC and amygdala. Based on previous differential activation in BPD versus healthy subjects,[18] planned contrasts of interest (COI) probing motor inhibitory control during negative versus neutral emotional processing were selected. COI were examined: (i) as a function of treatment ([*post-treatment scan* vs *pre-treatment scan*] × [*negative* vs *neutral*] × [*no-go* vs *go*]); and (ii) as predictors of treatment response (*pre-treatment scan*: [*negative* vs *neutral*] × [*no-go* vs *go*]) via correlations with TFP-related changes in MPQ-constraint, ALS-total and OAS-M. The statistical significance of the group-level comparison/interaction was assessed based on Gaussian Random Field theory as implemented in SPM. The group-level *t*-statistic map of a COI was initially thresholded at a voxel-wise *P*-value < 0.01 and a spatial extent >¼ cc. For an ROI, the predicted peaks were considered statistically significant if their initial voxel-wise *P*-value was <0.001 and family-wise-error-rate (FWE) corrected *P*-value was <0.05 over a sphere with a radius = 6.2 mm that resulted in a search volume of 1 cc.

RESULTS

Behavioral and treatment results

There were no statistically significant treatment-related effects with in-scanner task performance as measured by reaction times and commission/omission errors. Likewise, there were no statistically significant treatment-related effects on valence ratings and word recognition. Although not powered specifically to measure TFP-related clinical changes, statistically significant improvements were found post- versus pre-TFP in ALS-total ($P = 0.038$; pretreatment mean 48.30 ± 11.97; post-treatment mean 40.50 ± 11.28) and OAS-M ($P = 0.011$; pretreatment mean 13.92 ± 10.28; post-treatment score 6.67 ± 3.91) using repeated measures analysis of variance (ANOVA). Change in MPQ-constraint clinical scores was not statistically significant ($P = 0.324$; pretreatment mean 64.20 ± 13.82; post-treatment mean 68.40 ± 11.63).

Neuroimaging results

The COI probing the neural substrates of the interaction of negative (versus neutral) emotional processing and behavioral inhibition as a function of longitudinal TFP treatment was the three-way interaction term: ([*post-treatment scan* vs *pre-treatment scan*] × [*negative* vs *neutral*] × [*no-go* vs *go*]). In comparison to pre-treatment scans, BPD patients showed relative increased activation in cognitive control regions, including right anterior-dorsal ACC, dlPFC and FPC. Relative activation decreases were found in left ventrolateral PFC (vlPFC) (inferior frontal gyrus [*pars orbitalis* and *triangularis*]) and hippocampus (see Figure 1 and Supplemental Tables S2 and S3).

Correlational analyses assessed the association between clinical improvement in domains of interest following treatment and changes in neural activity during behavioral inhibition in the context of negative versus neutral emotional processing. With the three-way interaction contrast ([*post-treatment scan* vs *pre-treatment scan*] × [*negative* vs *neutral*] × [*no-go* vs *go*]), improvements in MPQ-constraint scores correlated positively with left anterior-dorsal ACC activation. Improvements in ALS-total correlated positively with left posterior-medial OFC/ventral striatum activation, and negatively with right amygdala/parahippocampal cortex activation (see Figure 2 and Supplemental Tables S2 and S4).

Neural predictors of treatment response were examined by correlating pre-treatment neural activation to changes in clinical scores using the two-way contrast: (*pre-treatment scan*: [*negative* vs *neutral*] × [*no-go* vs *go*]). Improvements in MPQ-constraint negatively correlated with pre-treatment right anterior-dorsal ACC activation. Improvement in ALS-total negatively correlated with left posterior-medial OFC/ventral striatum activation (see Figure 3 and Supplemental Tables S2 and S4).

DISCUSSION

This initial study examined changes in frontolimbic neural activity associated with TFP treatment in BPD patients while probing behavioral inhibition in the context of negative emotional processing. Based on our previously published neuroimaging findings in healthy[17] and BPD subjects,[18] along with psychological and neurobiological models of BPD,[27,28] we hypothesized treatment-related changes in prefrontal

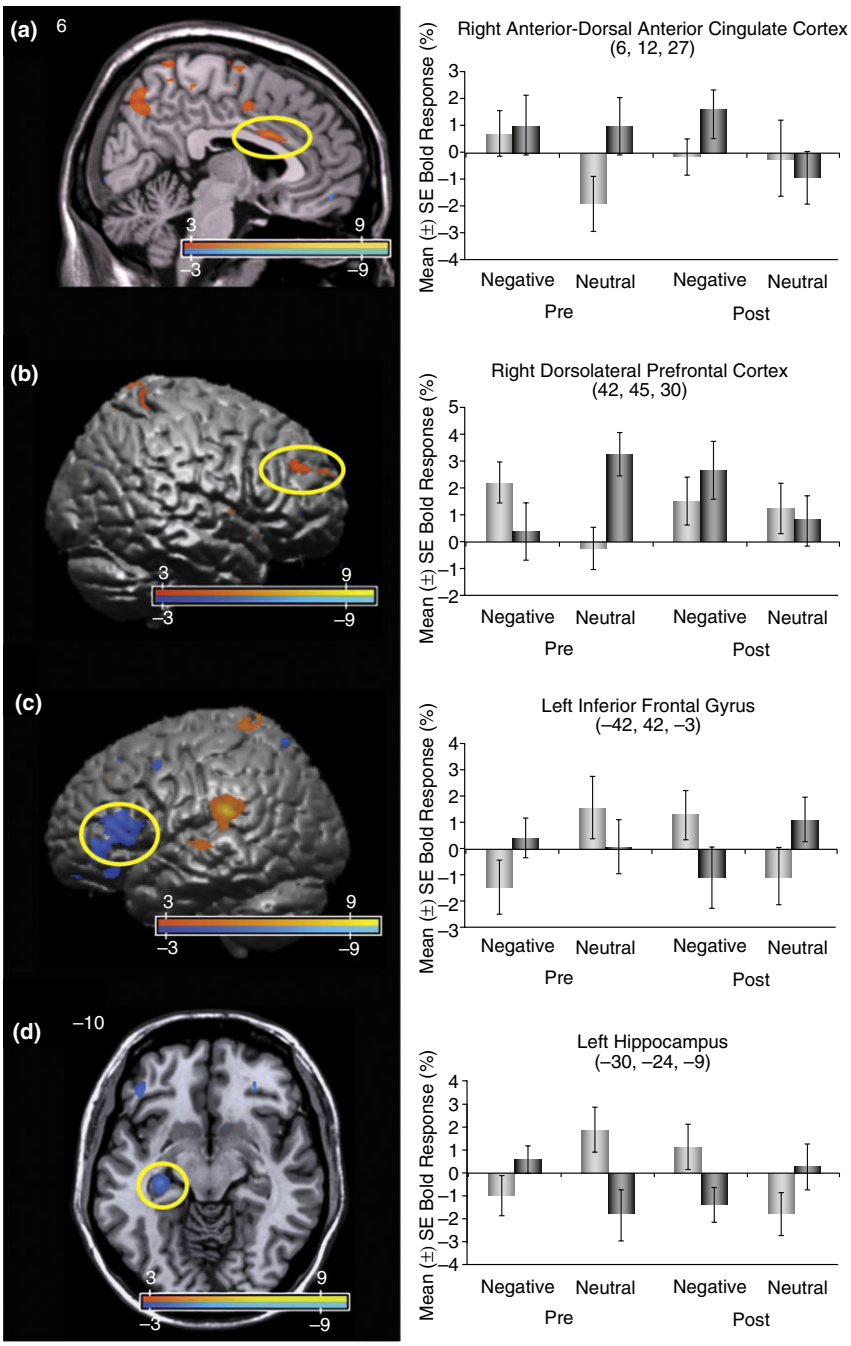

Figure 1. Increased dorsal anterior cingulate and dorsolateral prefrontal cortex activation and decreased inferior frontal gyrus and hippocampus activation during behavioral inhibition in the context of negative emotional processing post- vs pre-transference-focused psychotherapy (TFP). Panels (a)–(d) depict the interaction ([*post-treatment* vs *pre-treatment*] × [*negative* vs *neutral*] × [*no-go* vs *go*]) (Supplementary Table S2 and S3). Statistical parametric maps are thresholded at a voxelwise *P*-value of 0.01. Following treatment with TFP, borderline personality disorder patients demonstrated relative increased activation in the (a) right anterior-dorsal anterior cingulate cortex (voxel-wise *P*-value = 0.001; corrected *P*-value = 0.022) and the (b) right dorsolateral prefrontal cortex (voxel-wise *P*-value = 0.001); relative activation decreases following treatment were noted in the (c) left inferior frontal gyrus (voxel-wise *P*-value < 0.001) and the (d) left hippocampus (voxel-wise *P*-value = 0.001). (•) *Go*. (•) *No-go*.

and limbic regions as neural mechanisms associated with TFP-mediated clinical improvement.

Treatment with TFP was associated with relative activation increases in emotional and cognitive control areas and relative decreases in areas associated with emotional reactivity and semantic-based memory retrieval. These findings suggest that TFP may potentially facilitate symptom improvement in BPD, in part, by improving cognitive–emotional control via increased dorsal ACC, posterior-medial OFC, frontopolar, and dlPFC engagement. Baseline ACC dysfunction has been characterized in BPD across a number of affectively valenced paradigms.[3,4,9,10,12,18,19] The subgenual, perigenual and

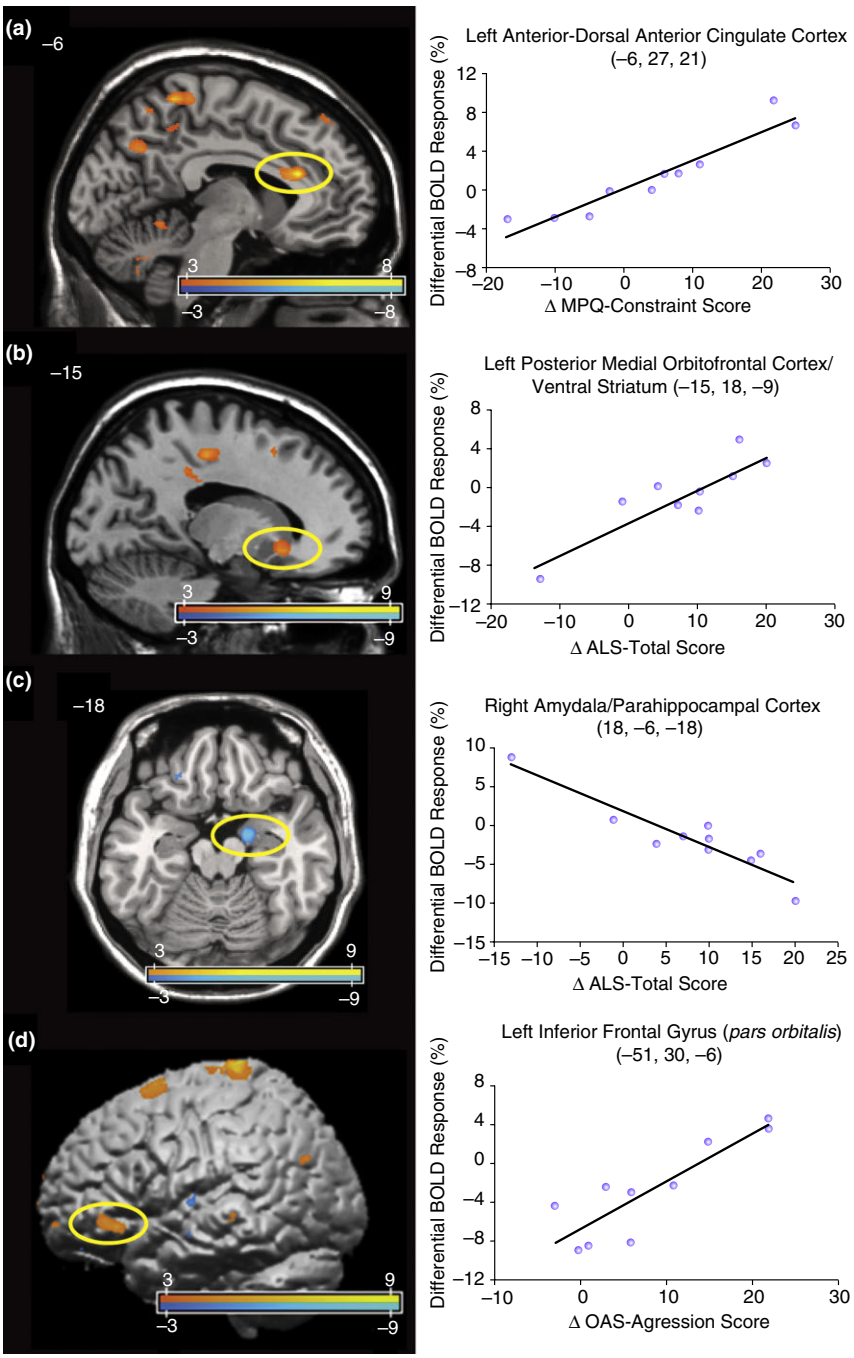

Figure 2. Dorsal anterior cingulate, posterior-medial orbitofrontal, amygdala, and inferior frontal gyrus activation changes post- vs pre-transference-focused psychotherapy correlated with clinical improvement. Panels (a)–(d) depict correlational analyses of post- vs pre-treatment-related effects on constraint, affective lability, and aggression for the interaction ([*post-treatment* vs *pre-treatment*] × [*negative* vs *neutral*] × [*no-go* vs *go*]) (Supplementary Table S2 and S4). Statistical parametric maps are thresholded at a voxelwise *P*-value of 0.01. Panel (a) shows a positive correlation between improvements in Multidimensional Personality Questionnaire (MPQ) – Constraint score and relative increased activation in the left anterior-dorsal anterior cingulate cortex (voxel-wise *P*-value < 0.001, corrected *P*-value = 0.002). Panel (b) shows a positive correlation between improvements in Affective Lability Scale (ALS) – Total score and relative increased activation in the left posterior-medial orbitofrontal cortex/ventral striatum (voxel-wise *P*-value = 0.001, corrected *P*-value = 0.028). Panel (c) shows a negative correlation between improvements in ALS-Total score and relative decreased activation in the right amygdala/parahippocampal cortex (voxel-wise *P*-value < 0.001, corrected *P*-value = 0.005). Panel (d) shows a positive correlation between improvements in Overt Aggression Scale-Modified (OAS-M) aggression score and relative increased activation in the left inferior frontal gyrus (voxel-wise *P*-value = 0.001). X-axes formatted so that increasing values reflect clinical improvement. BOLD, blood-oxygen-level-dependent.

anterior-dorsal ACC subregions are heavily interconnected with limbic regions, including the amygdala and hippocampus, while the anterior and posterior dorsal ACC subregions are interconnected to lateral prefrontal and premotor regions involved in higher-order executive and behavioral functions.[29] Based on structural connectivity, the anterior-dorsal ACC may be conceptualized as a critical node for the convergence of emotional regulation, cognitive control and behavioral expression. The anterior-dorsal ACC and dlPFC have been described as having regulatory efferent connections to the amygdala. TFP treatment was

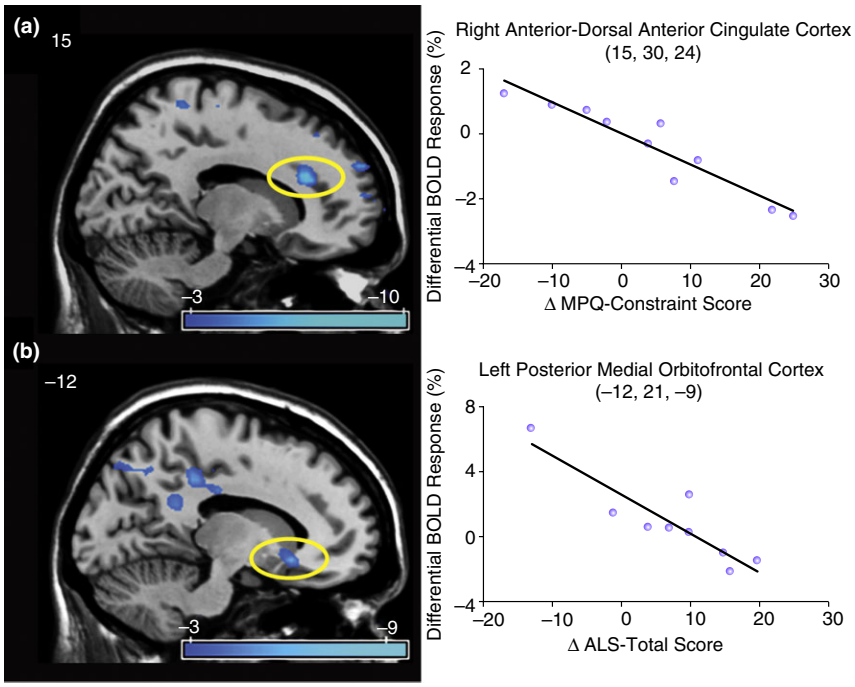

Figure 3. Pre-treatment dorsal anterior cingulate and posterior medial orbitofrontal activation negatively correlated with clinical improvement.
Panels (a)–(b) depict correlational analyses of pre-treatment-related effects on constraint and affective lability for the interaction (*pre-treatment*: [*negative* vs *neutral*] × [*no-go* vs *go*]) (Supplementary Table S2 and S4). Statistical parametric maps are thresholded at a voxelwise *P*-value of 0.01. Panel (a) shows an inverse correlation between pre-treatment activation in the right anterior-dorsal anterior cingulate cortex and post-treatment improvements in Multidimensional Personality Questionnaire (MPQ) – Constraint score (voxel-wise *P*-value < 0.001, corrected *P*-value = 0.002). Panel (b) shows an inverse correlation between pre-treatment activation in the left posterior-medial orbitofrontal cortex/ventral striatum and post-treatment improvements in Affective Lability Scale (ALS) – Total score (voxel-wise *P*-value < 0.001, corrected *P*-value = 0.013). X-axes formatted so that increasing values reflect clinical improvement. BOLD, blood-oxygen-level-dependent.

associated with relative increases in dorsal ACC and dlPFC activation following treatment. Post- versus pre-treatment anterior-dorsal ACC activation correlated positively with improvements in constraint, while reduced pre-treatment anterior-dorsal ACC activation predicted clinical improvement in constraint. The association between clinical improvement, low pre-treatment, and relatively elevated post-treatment anterior-dorsal ACC activation suggests that TFP may potentially modulate neural activity in this region to improve behavioral restraint.

Enhanced post- versus pre-treatment and blunted pre-treatment posterior-medial OFC activation positively correlated with improvement in affective lability. The medial OFC is implicated in emotion- and value-based decision-making, behavioral flexibility and choice maintenance, with medial/lateral functional distinctions based on anatomical connectivity suggesting that the medial OFC (and its ventral striatum connections) subserves behavioral responses in the context of viscerosomatic function, while lateral OFC mediates more sensory-based evaluations.[30] The posterior-medial OFC is particularly implicated in emotion regulation given its ACC, lateral PFC, amygdala, and hypothalamic connections.

In addition to modulation of medial PFC, TFP-associated amygdalar effects were also observed. Improvements in affective lability inversely correlated with post- versus pre-treatment right amygdala activation during behavioral inhibition in the context of negative emotional processing. The amygdala is critical for negative emotion and fear expression, salience, and emotional memory. Consistent with models of emotion and behavioral regulation, response to TFP was associated with increased dorsal

ACC and posterior-medial OFC activation, along with reduced amygdala activation. These frontolimbic activation patterns suggest that BPD patients were potentially able to engage in task demands with reduced negative emotional interference post-treatment.

Apart from hypothesized frontolimbic regions, potentially important treatment-related changes in the vlPFC and hippocampus were also noted (Supplemental Tables S3 and S4). Decreased left vlPFC (*pars orbitalis* and *pars triangularis*) activation (post- vs pre-treatment) was observed during the interaction between negative emotional processing and behavioral inhibition. Post-treatment, a positive correlation was observed between increased left vlPFC (*pars orbitalis*) activation and improvements in aggression; pre-treatment activation in the *pars orbitalis* and *triangularis* portions of the vlPFC predicted improvements in constraint and affective lability, respectively. The ventral and anterior portions of the left vlPFC (*pars orbitalis*) are interconnected with the medial temporal lobe and are implicated in cognitive control processes that guide access to relevant semantic memories by facilitating flexibility and integration between contextually meaningful representations of perceptual, mnemonic, and behavioral responses.[31] Given the observed role of the vlPFC with the current task and the recall bias for salient, negatively valenced information in BPD,[16] it might be hypothesized that treatment enabled a decreased need for goal-directed access to semantic information and that negative emotion was detected and controlled rapidly. Neutral stimuli were potentially interpreted more ambiguously and required additional evaluation. The observed positive correlation between *pars orbitalis* activation and improved aggression supports a relationship between cognitive control mechanisms and anger regulation. Posterior and dorsal portions of the vlPFC (*pars triangularis*) are implicated more in controlled semantic disambiguation en route to a behavioral response, facilitating controlled post-retrieval selection.[31] Following treatment, this portion of the vlPFC was also relatively less active in response to negative versus neutral words, suggesting automatic forms of semantic-level conflict resolution in the context of negative emotion. The association of pre-treatment activity in the *pars orbitalis* and *triangularis* with improved constraint and affective lability may further suggest that these regions of the vlPFC are associated with improvements in impulsivity and mood lability following TFP.

Decreased left hippocampal activation was also noted pre-to-post TFP treatment. The hippocampus is critical for rapid encoding, consolidation, and retrieval of contextual features. Consistent with relative decreased vlPFC activation, relative hippocampal activation decreases suggest a reduced need for semantic memory retrieval in the context of negative versus neutral emotion. In response to TFP, activation of the left hippocampus negatively correlated with improvement in affect lability and constraint, while pre-treatment hippocampal activation positively correlated with improvement in these symptom domains. In contrast, relative decreased hippocampal activation pre-treatment was predictive of improvements in measures of aggressive behavior. These results suggest potential differences in processing semantic memories associated with affective lability and constraint versus aggression that require further exploration.

We postulate that TFP treatment effects are primarily associated with top-down prefrontal control over limbic emotional reactivity and semantic memory processing systems. Another potential mechanism includes a cognitive form of semantic–linguistic modulation (many left-lateralized findings). This possible interpretation is consistent with a therapeutic model of TFP, which describes an engagement of the patient's 'observing ego' that leads to improved awareness of potentially threatening negative emotions and a renewed ability to integrate realistic representations of self and other.[20] The transference process is relational and may also engage social-cognitive systems. In addition, one may consider that TFP may potentially facilitate mechanisms of exposure, extinction, and reconsolidation in relation to challenging emotions and behavior enabling more adaptive associations and behaviors. These findings suggest that the dorsal ACC, posterior-medial OFC, vlPFC, amygdala and hippocampus warrant further investigation as potential biomarkers associated with clinical improvement following TFP treatment.

In a prior study of six BPD patients scanned before and after 12-weeks of dialectical behavioral therapy (DBT),[32] four individuals improved following DBT and displayed reduced amygdalar and hippocampal activation consistent with our findings. In a more recent 12-month post- versus pre-DBT neuroimaging study in 11 BPD patients and 11 healthy subjects, ROI analyses showed decreased amygdalar activa-

tion, and an association between post-treatment decreased amygdala activation and improvements in emotion regulation.[33] These studies suggest some shared mechanisms of treatment and/or correlates of symptom reductions. In addition, two other studies have probed neural activation changes related to psychodynamic psychotherapy (neither in BPD). Following 15 months of psychodynamic psychotherapy, 16 subjects with depression demonstrated reduced left amygdala and anterior hippocampal activation.[34] Similar normalization of pre-treatment elevated amygdalar and hippocampal activation following short-term, psychodynamic inpatient psychotherapy in panic disorder has also been characterized.[35] Furthermore, pre-treatment relative increases in dorsal ACC, medial OFC and dlPFC activation have predicted clinical response to cognitive–behavioral therapy.[36]

There are several limitations of this study. Our BPD cohort had multiple axis I and II psychiatric comorbidities and five subjects were on psychotropic medications that were not held constant throughout the TFP treatment intervention (including four subjects discontinuing anxiolytic medications). These confounds were only partially controlled for using a within-subjects design. While holding medications constant would have strengthened our ability to attribute activation changes to TFP, this is particularly challenging in BPD patients. The current study nonetheless advances our understanding of brain-symptom relationships related to links between neural activation changes and improvements in constraint and affective lability. The lack of a matched healthy control group also limited the ability to account for time-related scanner and other non-specific effects. While there is significant variability in the shape of BOLD responses collected across single subjects, it is important to note that the longitudinal stability of group activation maps in similarly robust cognitive tasks has been found to be reproducible and suitable for within-subjects designs.[37] Although the current findings are also limited by the small number of subjects and the interval range between scans (10–14 months), the delineation of clinically relevant neural activation changes related to psychodynamic psychotherapy have been scarcely studied to date.

In conclusion, this study provides preliminary empirical support for systems-level frontolimbic neural mechanisms and potential biomarkers associated with clinical improvements in patients with BPD following TFP. These results advance our currently limited understanding of neural mechanisms associated with psychodynamically oriented psychotherapy. Activation in the anterior-dorsal ACC, posterior-medial OFC, amygdala-hippocampus, and vlPFC was associated with improvements in behavioral constraint, emotional regulation and/or aggression in patients with BPD. Future research should seek to replicate these findings in a larger, controlled sample, and investigate hypoactivation of the anterior-dorsal ACC and posterior-medial OFC as possible endophenotypes linked to impulsivity and affective lability, respectively, in BPD and individuals at increased risk for developing BPD.

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REFERENCES

1. Clarkin JF, Levy KN, Lenzenweger MF, Kernberg OF. The Personality Disorders Institute/Borderline Personality Disorder Research Foundation randomized control trial for borderline personality disorder: Rationale, methods, and patient characteristics. *J. Pers. Disord.* 2004; **18**: 52–72.
2. Levy KN, Clarkin JF, Yeomans FE, Scott LN, Wasserman RH, Kernberg OF. The mechanisms of change in the treatment of borderline personality disorder with transference focused psychotherapy. *J. Clin. Psychol.* 2006; **62**: 481–501.
3. Minzenberg MJ, Fan J, New AS, Tang CY, Siever LJ. Frontolimbic dysfunction in response to facial emotion in borderline personality disorder: An event-related fMRI study. *Psychiatry Res.* 2007; **155**: 231–243.
4. Wingenfeld K, Rullkoetter N, Mensebach C *et al*. Neural correlates of the individual emotional Stroop in borderline personality disorder. *Psychoneuroendocrinology* 2009; **34**: 571–586.
5. Kraus A, Valerius G, Seifritz E *et al*. Script-driven imagery of self-injurious behavior in patients with borderline per-

sonality disorder: A pilot FMRI study. *Acta Psychiatr. Scand.* 2010; **121**: 41–51.
6. Schulze L, Domes G, Kruger A *et al*. Neuronal correlates of cognitive reappraisal in borderline patients with affective instability. *Biol. Psychiatry* 2011; **69**: 564–573.
7. Donegan NH, Sanislow CA, Blumberg HP *et al*. Amygdala hyperreactivity in borderline personality disorder: Implications for emotional dysregulation. *Biol. Psychiatry* 2003; **54**: 1284–1293.
8. Herpertz SC, Dietrich TM, Wenning B *et al*. Evidence of abnormal amygdala functioning in borderline personality disorder: A functional MRI study. *Biol. Psychiatry* 2001; **50**: 292–298.
9. Niedtfeld I, Schulze L, Kirsch P, Herpertz SC, Bohus M, Schmahl C. Affect regulation and pain in borderline personality disorder: A possible link to the understanding of self-injury. *Biol. Psychiatry* 2010; **68**: 383–391.
10. Kamphausen S, Schroder P, Maier S *et al*. Medial prefrontal dysfunction and prolonged amygdala response during instructed fear processing in borderline personality disorder. *World J. Biol. Psychiatry* 2013; **14**: 307–318, S1–4.
11. Hazlett EA, Zhang J, New AS *et al*. Potentiated amygdala response to repeated emotional pictures in borderline personality disorder. *Biol. Psychiatry* 2012; **72**: 448–456.
12. Cullen KR, Vizueta N, Thomas KM *et al*. Amygdala functional connectivity in young women with borderline personality disorder. *Brain Connect.* 2011; **1**: 61–71.
13. McCloskey MS, New AS, Siever LJ *et al*. Evaluation of behavioral impulsivity and aggression tasks as endophenotypes for borderline personality disorder. *J. Psychiatr. Res.* 2009; **43**: 1036–1048.
14. Rentrop M, Backenstrass M, Jaentsch B *et al*. Response inhibition in borderline personality disorder: Performance in a Go/Nogo task. *Psychopathology* 2008; **41**: 50–57.
15. Lenzenweger MF, Clarkin JF, Fertuck EA, Kernberg OF. Executive neurocognitive functioning and neurobehavioral systems indicators in borderline personality disorder: A preliminary study. *J. Pers. Disord.* 2004; **18**: 421–438.
16. Korfine L, Hooley JM. Directed forgetting of emotional stimuli in borderline personality disorder. *J. Abnorm. Psychol.* 2000; **109**: 214–221.
17. Goldstein M, Brendel G, Tuescher O *et al*. Neural substrates of the interaction of emotional stimulus processing and motor inhibitory control: An emotional linguistic go/no-go fMRI study. *Neuroimage* 2007; **36**: 1026–1040.
18. Silbersweig D, Clarkin JF, Goldstein M *et al*. Failure of frontolimbic inhibitory function in the context of negative emotion in borderline personality disorder. *Am. J. Psychiatry* 2007; **164**: 1832–1841.
19. Jacob GA, Zvonik K, Kamphausen S *et al*. Emotional modulation of motor response inhibition in women with borderline personality disorder: An fMRI study. *J. Psychiatry Neurosci.* 2013; **38**: 164–172.
20. Kernberg OF, Yeomans FE, Clarkin JF, Levy KN. Transference focused psychotherapy: Overview and update. *Int. J. Psychoanal.* 2008; **89**: 601–620.
21. Clarkin JF, Levy KN, Lenzenweger MF, Kernberg OF. Evaluating three treatments for borderline personality disorder: A multiwave study. *Am. J. Psychiatry* 2007; **164**: 922–928.
22. Loranger AW, Sartorius N, Andreoli A *et al*. The International Personality Disorder Examination. The World Health Organization/Alcohol, Drug Abuse, and Mental Health Administration international pilot study of personality disorders. *Arch. Gen. Psychiatry* 1994; **51**: 215–224.
23. Clarkin JF, Yeoman FE, Kernberg OF. *Psychotherapy for Borderline Personality*. John Wiley & Sons, New York, 1999.
24. Tellegen A. *Brief Manual for the Multidimensional Personality Questionnaire*. University of Minnesota, Minneapolis, MN, 1982.
25. Harvey PD, Greenberg BR, Serper MR. The affective lability scales: Development, reliability, and validity. *J. Clin. Psychol.* 1989; **45**: 786–793.
26. Coccaro EF, Harvey PD, Kupsaw-Lawrence E, Herbert JL, Bernstein DP. Development of neuropharmacologically based behavioral assessments of impulsive aggressive behavior. *J. Neuropsychiatry Clin. Neurosci.* 1991; **3**: S44–S51.
27. Clarkin JF, De Panfilis C. Developing conceptualization of borderline personality disorder. *J. Nerv. Ment. Dis.* 2013; **201**: 88–93.
28. Brendel GR, Stern E, Silbersweig DA. Defining the neurocircuitry of borderline personality disorder: Functional neuroimaging approaches. *Dev. Psychopathol.* 2005; **17**: 1197–1206.
29. Etkin A, Egner T, Kalisch R. Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends Cogn. Sci.* 2011; **15**: 85–93.
30. Ongur D, Price JL. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cereb. Cortex* 2000; **10**: 206–219.
31. Badre D, Wagner AD. Left ventrolateral prefrontal cortex and the cognitive control of memory. *Neuropsychologia* 2007; **45**: 2883–2901.
32. Schnell K, Herpertz SC. Effects of dialectic-behavioral-therapy on the neural correlates of affective hyperarousal in borderline personality disorder. *J. Psychiatr. Res.* 2007; **41**: 837–847.
33. Goodman M, Carpenter D, Tang CY *et al*. Dialectical behavior therapy alters emotion regulation and amygdala activity in patients with borderline personality disorder. *J. Psychiatr. Res.* 2014; **57**: 108–116.
34. Buchheim A, Viviani R, Kessler H *et al*. Changes in prefrontal-limbic function in major depression after 15 months of long-term psychotherapy. *PLoS ONE* 2012; **7**: e33745.
35. Beutel ME, Stark R, Pan H, Silbersweig D, Dietrich S. Changes of brain activation pre- post short-term psycho-

dynamic inpatient psychotherapy: An fMRI study of panic disorder patients. *Psychiatry Res.* 2010; **184**: 96–104.
36. Gabrieli JD, Ghosh SS, Whitfield-Gabrieli S. Prediction as a humanitarian and pragmatic contribution from human cognitive neuroscience. *Neuron* 2015; **85**: 11–26.
37. Plichta MM, Schwarz AJ, Grimm O *et al*. Test-retest reliability of evoked BOLD signals from a cognitive-emotive fMRI test battery. *Neuroimage* 2012; **60**: 1746–1758.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Supplemental Figure 1. Schematic figure of the emotional-linguistic *go/no-go* task and timing parameters.
Supplemental Table S1. Demographic and clinical information for the 10 recruited patients with borderline personality disorder.
Supplemental Table S2. Region of interest (ROI) analyses of brain regions showing differential blood-oxygen-level-dependent (BOLD) neural activation in borderline personality disorder patients post- vs pre-treatment for the interaction effect between negative (versus neutral) emotional words and *no-go* (versus go) conditions ([*post-treatment scan* vs *pre-treatment scan*] × [*negative* vs *neutral*] × [*no-go* vs *go*]) shown in Figure 1. ROI analyses showing post vs pre-treatment and pre-treatment effects correlated to clinical improvement in constraint (Multidimensional Personality Questionnaire-Constraint), and affective lability (Affective Lability Scale-Total) shown in Figures 2 and 3.
Supplemental Table S3. Brain regions showing differential blood-oxygen-level-dependent (BOLD) neural activation in borderline personality disorder patients post- vs pre-treatment for the interaction effect between negative (versus neutral) emotional words and *no-go* (versus go) conditions ([*post-treatment scan* vs *pre-treatment scan*] × [*negative* vs *neutral*] × [*no-go* vs *go*]) (See also Supplemental Table S2 and Fig. 1).
Supplemental Table S4. Brain regions showing post- vs pre-treatment and pre-treatment effects correlated to clinical improvement in constraint (Multidimensional Personality Questionnaire-Constraint), affective lability (Affective Lability Scale-Total) and aggression (Overt Aggression Scale-Modified) (See also Supplemental Table S2 and Figs 2 and 3).

Supplemental Methods.

Data Acquisition: Imaging data were acquired pre- and post-TFP with a GE Signa 3Tesla MRI scanner (General Electric Company, Waukesha, Wisc.; maximum gradient strength 40 mT/m, maximum gradient slew rate 150 T/m per sec). For both pre- and post-TFP scanning sessions, structural images were acquired with a three-dimensional high-resolution T1-weighted spoiled gradient (SPGR) recalled acquisition sequence (TE/TR=8/30msec, flip angle=45, field of view=220mm, 140 coronal slices with thickness=contiguous 1.5mm, number of averages=1, matrix=256x256, voxel resolution=0.8594x1.5x0.8594mm^3). Before fMRI runs, a reference T1-weighted anatomical image with the same axial slice placement and thickness as the functional imaging was acquired with two slices centered within the amygdala (256x256 matrix size, 5mm in thickness, 1mm gap, TE/TR=14/500ms, FoV=240mm). Echo planar imaging (EPI) was used to obtain blood-oxygen-level-dependent (BOLD) functional MR images. After shimming to maximize homogeneity, a series of functional scans were collected using a gradient echo EPI sequence (TE/TR=30/1200msec, flip angle=70°, FoV=240 mm, 21 slices with thickness=5 mm, interslice distance=1 mm, matrix=64×64), with a z-shimming algorithm to reduce susceptibility artifact in ventral brain regions of interest.

Functional Image Processing: Similar to Silbersweig et al., 2007, the functional image processing pipeline consisted of the following steps using customized SPM software carried out on an UNIX server (Sun Microsystems, Mountainview, CA): manual AC-PC re-orientation of the two T1 anatomical images (high-resolution SPGR and in-plane reference) was performed for both scan dates, and transformation parameters of the reference T1 image on each scan date were applied (as the proxy of the first functional EPI-BOLD image) to all the functional EPI-BOLD images on the same date; realignment to correct for slight head movement between functional

scans based on intracranial voxels was performed, and all the resulting realigned images from both scan dates were in the space of the reference T1 image of the first scan date (Note: there was no apparent head-motion of more than one voxel size over the entire scan length at a given scan date for a given subject detected by the realignment algorithm, due to the fact that a custom-made head-holder helmet was used to minimize any potential head-motion during the fMRI acquisition on all the scanning sessions through the entire study, and all the subjects were specifically instructed before each functional run to hold their head and body still); co-registration of functional EPI-BOLD images to the corresponding high-resolution T1 SPGR anatomical image of the first scan date was performed, and based on the rigid body transformation parameters from the reference T1 image (as the proxy of the first functional EPI-BOLD image) of the first scan date to the T1 SPGR image of the first scan date for each individual subject; stereotactic normalization to a standardized coordinate space (Montreal MRI Atlas version of Talairach space) was based on the high-resolution T1 SPGR anatomical image of the first scan date to normalize for individual differences in brain morphology, and the normalization transformation to all realigned and co-registered functional EPI-BOLD images was applied; spatial smoothing of all the normalized functional EPI-BOLD images used an isotropic Gaussian kernel (FWHM=7.5mm).

Functional Image Analysis: A two-level voxel-wise linear random-effects model was utilized to examine the effect sizes of the key Group/Condition contrasts in a repeated-measures ANCOVA setting. First, a voxel-wise multiple linear regression model was employed at the individual subject level. This comprised of the block-by-block/trial-by-trial regressors of interest, which consisted of the condition onset times convolved with a prototypical hemodynamic

response function, and the covariates of no interest, which consisted of the temporal first-order derivative of the principal regressors (to compensate for slight latency differences in individual hemodynamic response from the prototypical response function), global fluctuations, realignment parameters, and scanning periods. Temporal filtering was performed to counter the effects of baseline shifts and higher frequency noise (than prototypical hemodynamic response), and an AR(1) model of the time course was used to accommodate temporal correlation in consecutive scans. Effect at every brain voxel was estimated using the EM (expectation maximization) algorithm, and regionally specific effects were then compared using linear contrasts. That is, for each subject, the effect image for each condition was calculated, and was also combined in a series of linear contrasts to be entered into the second level group analysis to assess within-group effect sizes of the key hypotheses. Second, at the group level, a random-effects model was used (with the subject factor as the random-effect), which accounted for inter-subject variability. The within-group effects of the hypothesis-driven contrasts was then estimated using an EM algorithm, with age incorporated as a covariate of no interest. These group-level effect estimates generated statistical maps of the t-statistic, and the statistical significance of the t-maps was then evaluated in the final step of inference. The statistical inference was based on random field theory as implemented in SPM, where voxel-wise p-values were corrected based on family-wise error rate of the voxel values within an ROI.

Supplemental Figure 1. Schematic figure of the emotional-linguistic *go/no-go* task and timing parameters. **A**. A total of 192 distinct linguistic stimuli were used (64 negative, 64 positive, 64 neutral). Words were balanced across all valence conditions for frequency, word length, part of speech, and imageability. The task was presented in a block design comprising 24 blocks (6 blocks/run, 4 runs total). Each of the 6 blocks represented the six main conditions (negative go, negative no-go, neutral go, neutral no-go, positive go, positive no-go), the presentation of which was counterbalanced to control for order and time effects across runs. Go blocks contained 16 go trials (100% go trials), and no-go blocks contained 10 go trials (62.5% go trials) and 6 no-go trials (37.5% no-go trials), presented in pseudorandomized order to establish prepotent motor responses. For clarity only one of the 4 runs is shown. Subjects were instructed to perform a right index finger button-press immediately after silently reading a word appearing in normal font (go trial) and to inhibit this response after reading a word in italicized font (no-go trial). **B.** Two representative blocks are shown to illustrate timing parameters. Each word was presented individually in white letters on a dark background for 1.5 sec followed by a 0.75-sec interstimulus interval (total block duration=36 sec). Each block was followed by a 20-sec rest period during which a fixation cross was displayed. Stimulus presentation and response collection were performed within the Integrated Functional Imaging System SA/E-Prime environment (MRI Devices Corporation, Waukesha, Wisc.; Psychology Software Tools, Inc., Pittsburgh, PA.).

Supplemental Table 1. Demographic and clinical information for the 10 recruited patients with borderline personality disorder.

Subject	Age	Handedness	Education	TFP Duration (months)	Pre-TFP Meds	Post-TFP Meds
1	32	R	Some College	12	None	LTG
2	27	L	College Degree	12	BUP, DXAM	BUP
3	28	R	College Degree	10	OCP	Fish Oil
4	25	R	Some College	12	DXAM/AMP, APZ, ECP	ATX, TPM
5	29	R	College Degree	12	SERT, TPM, TZD, CLP	None
6	24	R	College Degree	12	OCP	None
7	28	R	College Degree	13	None	None
8	30	R	Some College	14	LTG, DLX, CLP, OXY, BTA	LTG, SERT, MPH, OXY
9	23	R	High School Degree	12	FLUX, DZP, DPH	FLUX
10	32	R	College Degree	12	None	None

The planned duration of the study treatment period was 12 months. One patient ended treatment 2 months early because she moved out of the country. One patient was difficult to schedule for the post-treatment fMRI so she was scanned at 14-months, but had continued to see her TFP therapist. Individuals with comorbid schizophrenia, schizoaffective disorder, bipolar I disorder, delusional disorder, delirium, and/or dementia were excluded, and none of the participants had significant medical/neurological conditions. R indicates right; L, left; TFP, transference-focused psychotherapy; BUP, buproprion, DXAM, dextroamphetamine; OCP, oral contraceptives; AMP, amphetamine, APZ, alprazolam; ECP, escitalopram; SERT, sertraline; TPM, topiramate; TZD, trazodone; CLP, clonazepam; LTG, lamotrigine; DLX, duloxetine; OXY, oxycodone; BTA,

butalbital; FLUX, fluoxetine; DZP, diazepam; DPH, diphenhydramine; ATX, atomoxetine; MPH, morphine.

Supplemental Table 2. Region of interest (ROI) analyses of brain regions showing differential blood-oxygen-level-dependent (BOLD) neural activation in borderline personality disorder patients post vs. pre-treatment for the interaction effect between negative (versus neutral) emotional words and nogo (versus go) conditions [(*post-treatment scan vs. pre-treatment scan*) × (*negative vs. neutral*) × (*nogo vs. go*)] shown in Figure 1. ROI analyses showing post vs. pre-treatment and pre-treatment effects correlated to clinical improvement in constraint (Multidimensional Personality Questionnaire-Constraint), and affective lability (Affective Lability Scale-Total) shown in Figures 2 and 3.

Comparison and Brain Region	**Brodmann Area**	**Peak Coordinate in MNI space (mm)**			**Peak voxel z-score**	**Peak voxel p-value (corrected p-value)**	**Cluster Extent (mm^3)**
		x	**y**	**z**			
Main Interaction: [(*Post-Treatment scan vs. Pre-Treatment scan*) × (*Negative vs. Neutral*) × (*NoGo vs. Go*)]							
Relative increased activity R anterior dorsal anterior cingulate cortex	24	6	12	27	3.19	0.001 (0.022*)	675
Contrast Correlated with Differential Clinical Score							
Multidimensional Personality Questionnaire (Constraint): [(*Post-Treatment scan vs. Pre-Treatment scan*) × (*Negative vs. Neutral*) × (*NoGo vs. Go*)]							
Positively correlated regions L anterior dorsal anterior cingulate cortex	24/32	-6	27	21	4.14	<0.001 (0.002*)	891
Affective Lability Scale (Total): [(*Post-Treatment scan vs. Pre-Treatment scan*) × (*Negative vs. Neutral*) × (*NoGo vs. Go*)]							
Positively correlated regions L posterior medial orbitofrontal cortex/ ventral striatum	11/25	-15	18	-9	3.14	0.001 (0.028*)	675
Negatively correlated regions R amygdala/ parahippocampal cortex	34/28	18	-6	-18	-3.87	<0.001 (0.005*)	1053
Multidimensional Personality Questionnaire (Constraint): [*Pre-Treatment scan*: (*Negative vs. Neutral*) × (*NoGo vs. Go*)]							
Negatively correlated regions R anterior dorsal anterior cingulate cortex	32	15	30	24	-4.18	<0.001 (0.002*)	972
Affective Lability Scale (Total): [*Pre-Treatment scan*: (*Negative vs. Neutral*) × (*NoGo vs. Go*)]							
Negatively correlated regions L posterior medial orbitofrontal cortex/ ventral striatum	11	-12	21	-9	-3.47	<0.001 (0.013*)	810

Note: Initial voxel-wise p-value < 0.01 with a minimal spatial extent of cluster > ¼ cc; *the peak voxel in a region-of-interest at FWE corrected p<0.05. L = left; R = right.

Supplemental Table 3. Brain regions showing differential blood-oxygen-level-dependent (BOLD) neural activation in borderline personality disorder patients post vs. pre-treatment for the interaction effect between negative (versus neutral) emotional words and nogo (versus go) conditions [(*post-treatment scan vs. pre-treatment scan*) × (*negative vs. neutral*) × (*nogo vs. go*)] (See also Supplemental Table 2 and Figure 1).

Comparison and Brain Region	**Brodmann Area**	**Peak Coordinate in MNI space (mm)**			**Peak voxel z-score**	**Peak voxel p-value (corrected p-value)**	**Cluster Extent (mm^3)**
		x	**y**	**z**			
Comparison: [(*Post-Treatment scan vs. Pre-Treatment scan*) × (*Negative vs. Neutral*) × (*NoGo vs. Go*)]							
Relative increased activity							
R anterior dorsal anterior cingulate cortex	**24**	**6**	**12**	**27**	**3.19**	**0.001 (0.022*)**	**675**
L middle cingulate cortex/ posterior dorsal anterior cingulate cortex	24	-12	0	45	4.61	<0.001	1782
R middle cingulate cortex/ posterior dorsal anterior cingulate cortex	24	9	0	45	3.35	<0.001	756
R middle frontal gyrus/ dorsolateral prefrontal cortex	46	42	45	30	3.12	0.001	621
R amygdala/ parahippocampal cortex	*36*	*30*	*6*	*-27*	*2.98*	*0.001*	*243*
R middle frontal gyrus/ frontopolar cortex	10	24	60	27	3.16	0.001	783
L superior temporal gyrus/ temporal parietal junction	42	-63	-33	21	4.45	<0.001	6831
L postcentral gyrus	3	-21	-33	60	3.66	<0.001	5454
R precuneus	5/7	9	-69	54	3.42	<0.001	5805
R precentral gyrus	6	24	-18	57	3.65	<0.001	1107
R supplemental motor area	6	6	-12	75	3.68	<0.001	351
Relative decreased activity							
L inferior frontal gyrus (pars orbitalis/ pars triangularis)	45/46/47	-42	42	-3	-3.57	<0.001	6318
L hippocampus	20	-30	-24	-9	-3.10	0.001	1350
L posterior orbitofrontal cortex	*11*	*-21*	*12*	*-21*	*-2.98*	*0.001*	*324*
R lateral orbitofrontal cortex	11	30	36	-15	-3.57	<0.001	270
L precentral gyrus/ premotor cortex	6	-51	9	51	-3.15	0.001	513
L superior parietal lobule	7	-27	-69	63	-3.15	0.001	324

Note: Initial voxel-wise p-value < 0.01 with a minimal spatial extent of cluster > ¼ cc; ***the peak voxel in an ROI at initial voxel-wise p < 0.001 and FWE corrected p<0.05**. Subthresholding trends in additional ROIs (the voxel-wise p-value at the peak voxel 0.001<p<0.01 and/or the cluster extent < ¼ cc) are listed in italic font, for the purpose of showing the direction/sign of the activations. L = left; R = right.

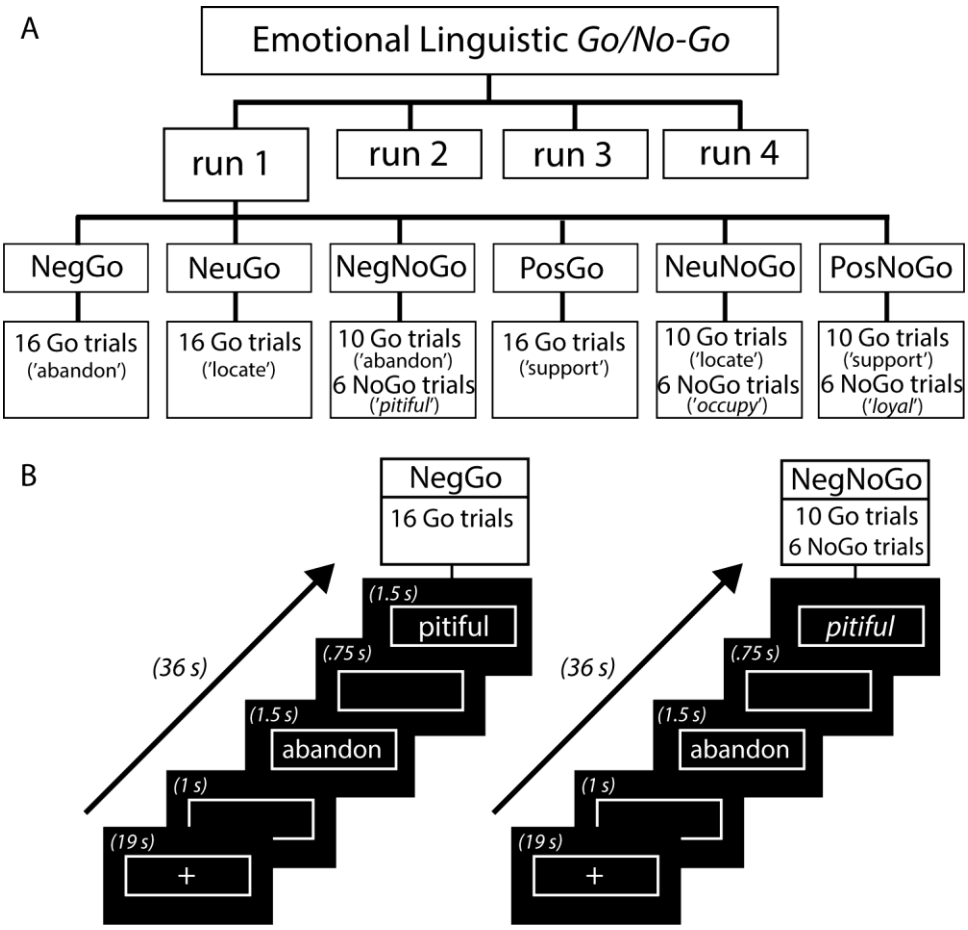
Supplemental Table 4. Brain regions showing post vs. pre-treatment and pre-treatment effects correlated to clinical improvement in constraint (Multidimensional Personality Questionnaire-Constraint), affective lability (Affective Lability Scale-Total) and aggression (Overt Aggression Scale-Modified) (See also Supplemental Table 2 and Figures 2 and 3).

Brain Region / Contrast Correlated with Differential Clinical Score	Brodmann Area	Peak Coordinate in MNI space (mm)			Peak voxel z-score	Peak voxel p-value (corrected p-value)	Cluster Extent (mm^3)
		x	y	z			
Multidimensional Personality Questionnaire (Constraint): [(*Post-Treatment scan vs. Pre-Treatment scan*) × (*Negative vs. Neutral*) × (*NoGo vs. Go*)]							
Positively correlated regions							
L anterior dorsal anterior cingulate cortex	**24/32**	**-6**	**27**	**21**	**4.14**	**<0.001 (0.002*)**	**891**
R anterior dorsal anterior cingulate cortex	*32*	*12*	*27*	*21*	*2.81*	*0.003*	*270*
L pregenual anterior cingulate cortex	*32*	*-12*	*36*	*12*	*3.05*	*0.001*	*270*
R pregenual anterior cingulate cortex	32	12	48	15	3.39	<0.001	1161
R superior frontal gyrus/ frontopolar cortex	10	21	57	12	3.95	<0.001	(above)
L superior frontal gyrus/ frontopolar cortex	10	-18	57	6	3.49	<0.001	756
R anterior medial orbitofrontal cortex	11	3	66	-15	3.45	<0.001	999
L superior frontal gyrus/ dorsolateral prefrontal cortex	32/9	-12	27	45	3.17	0.001	459
L precuneus	7	-3	-63	39	3.34	<0.001	3537
R supplementary motor area	4	3	-21	72	3.84	<0.001	1269
L anterior inferior temporal gyrus	20	-51	-9	-30	3.72	<0.001	324
R posterior middle temporal gyrus	21	63	-36	-3	3.50	<0.001	1593
R angular gyrus	39	39	-60	27	3.46	<0.001	999
L superior middle frontal gyrus/frontal eye fields	8	0	45	54	3.24	0.001	999
R cerebellum vermis 8		3	-63	-30	3.13	0.001	540
R paracentral lobule	5	9	-39	63	3.83	<0.001	3618
L middle temporal gyrus	21	-66	-57	18	3.63	<0.001	459
Negatively correlated regions							
L inferior frontal gyrus (pars triangularis)	45/46	33	27	27	-3.16	0.001	1026
L hippocampus	27	-15	-36	3	-3.42	<0.001	756
R thalamus		9	-18	12	-3.42	<0.001	2538
L thalamus		-18	-15	3	-3.37	<0.001	594
L anterior superior temporal gyrus	38	-51	0	-3	-3.84	<0.001	2322
R posterior superior temporal gyrus	42	60	-39	24	-3.36	<0.001	1242
R middle frontal gyrus/ supplementary motor and pre-motor cortex	6	39	-3	63	-3.47	<0.001	378
R visual association cortex	19	36	-78	33	-3.72	<0.001	972
L visual association cortex	19	-27	-60	30	-3.42	<0.001	675
R fusiform gyrus	37	39	-42	-18	-3.18	0.001	513
R supramarginal gyrus	40	54	-36	45	-3.36	<0.001	1350
R superior frontal gyrus/ frontal eye fields	8	21	9	51	-3.10	0.001	1485
Affective Lability Scale (Total): [(*Post-Treatment scan vs. Pre-Treatment scan*) × (*Negative vs. Neutral*) × (*NoGo vs. Go*)]							
Positively correlated regions							
L posterior medial orbitofrontal cortex/ ventral striatum	**11/25**	**-15**	**18**	**-9**	**3.14**	**0.001 (0.028*)**	**675**
R anterior dorsal anterior cingulate cortex	*32*	*9*	*33*	*24*	*2.57*	*0.005*	*513*
L anterior dorsal anterior cingulate cortex	*24*	*-3*	*21*	*36*	*3.01*	*0.001*	*351*
R inferior frontal gyrus (pars triangularis)	*45*	*39*	*36*	*0*	*3.06*	*0.001*	*135*
R frontal operculum	47	27	33	0	3.58	<0.001	1161
L middle cingulate gyrus	23	-15	-24	48	3.40	<0.001	621
L posterior cingulate gyrus	23	-12	-33	36	3.41	<0.001	540
L middle frontal gyrus/ dorsolateral prefrontal cortex	46	-24	39	27	3.80	<0.001	621
R superior frontal gyrus/ frontal eye fields	8	21	21	60	3.77	<0.001	834
L inferior temporal gyrus	20	-42	-33	-30	3.73	<0.001	351
L precentral gyrus	44	-33	9	33	3.72	<0.001	918
R cerebellum		9	-39	-36	3.34	<0.001	270

Negatively correlated regions							
R amygdala/ parahippocampal cortex	**34/28**	**18**	**-6**	**-18**	**-3.87**	**<0.001 (0.005*)**	**1053**
L hippocampus	*20*	*-24*	*-15*	*-9*	*-2.77*	*0.003*	*621*
L inferior frontal gyrus (pars triangularis)	45	-45	33	9	-3.52	<0.001	162
R postcentral gyrus	6/43	57	0	24	-3.57	<0.001	2943
R precentral gyrus	6	21	-15	57	-3.56	<0.000	270
L anterior middle temporal gyrus	21	-54	3	-27	-4.33	<0.001	1404
R superior temporal gyrus	22	63	-36	9	-3.21	0.001	405
R calcarine cortex	17	15	-81	3	-3.13	0.001	621
Overt Aggression Scale (Aggression): [(*Post-Treatment scan vs. Pre-Treatment scan*) × (*Negative vs. Neutral*) × (*NoGo vs. Go*)]							
Positively correlated regions							
L inferior frontal gyrus (pars orbitalis)	47	-51	30	-6	3.24	0.001	1080
L posterior orbitofrontal cortex		*-24*	*12*	*-15*	*2.81*	*0.002*	*108*
R posterior medial orbitofrontal cortex	*11/25*	*12*	*27*	*-3*	*2.78*	*0.003*	*324*
R ventral striatum		*18*	*18*	*-6*	*2.65*	*0.004*	*297*
L middle cingulate cortex		-9	-30	42	3.25	0.001	864
L postcentral gyrus	4	-12	-36	81	3.99	<0.001	2619
L superior frontal gyrus/ pre-motor cortex/ supplementary motor area	6	-24	12	69	3.45	<0.001	2457
Negatively correlated regions							
R amygdala	*34*	*27*	*6*	*-18*	*-2.72*	*0.003*	*81*
R hippocampus/ amygdala	*28/34*	*24*	*-3*	*-18*	*-2.45*	*0.007*	*81*
R gyrus rectus/ medial orbitofrontal cortex	*11*	*9*	*36*	*-15*	*-3.14*	*0.001*	*162*
R middle frontal gyrus/ dorsolateral prefrontal cortex	9	33	12	51	-3.51	<0.001	999
R middle frontal gyrus/ dorsolateral prefrontal cortex	9	24	27	33	-3.10	0.001	648
Cerebellar vermis 4,5		0	-51	3	-4.12	<0.001	5211
R Heschl's gyrus		48	-21	12	-3.34	<0.001	1863
R posterior superior temporal gyrus	22	66	-45	9	-3.32	<0.001	2565
L cerebellar vermis 10		-6	-48	-27	-4.32	<0.001	4077
Multidimensional Personality Questionnaire (Constraint): [*Pre-Treatment scan*: (*Negative vs. Neutral*) × (*NoGo vs. Go*)]							
Positively correlated regions							
R posterior dorsal anterior cingulate cortex	24	6	3	30	4.46	<0.001	1242
L hippocampus	*27*	*-15*	*-33*	*3*	*3.08*	*0.001*	*5805*
L thalamus		-21	-15	3	4.05	<0.001	(above)
R thalamus		12	-6	6	4.00	<0.001	6453
R extended amygdala		*30*	*12*	*-12*	*2.70*	*0.004*	*486*
L inferior frontal gyrus (pars triangularis)	45	-39	30	27	3.28	0.001	1215
R inferior frontal gyrus (pars orbitalis)	*47*	*36*	*30*	*-9*	*2.90*	*0.002*	*243*
L anterior insula		-42	12	-3	3.46	<0.001	2673
L Heschl's gyrus		-45	-18	3	3.79	<0.001	1296
L posterior superior/ middle temporal gyrus	22	-60	-36	9	3.40	<0.001	594
R posterior superior temporal gyrus/ temporoparietal junction	41	51	-36	24	3.60	<0.001	3348
R anterior superior temporal gyrus	38	54	3	-3	3.42	<0.001	864
L visual association cortex	19	-30	-66	33	3.11	0.001	540
L fusiform gyrus	37	-30	-60	-18	3.40	<0.001	270
Negatively correlated regions							
R anterior dorsal anterior cingulate cortex	**32**	**15**	**30**	**24**	**-4.18**	**<0.001 (0.002*)**	**972**
L subgenual anterior cingulate cortex	*25*	*0*	*21*	*-6*	*-2.83*	*0.002*	*135*
R middle frontal gyrus/ dorsolateral prefrontal cortex	*46*	*42*	*27*	*42*	*-2.76*	*0.003*	*378*
R lateral prefrontal cortex	46/47	48	51	-6	-3.27	0.001	351
L superior frontal gyrus/ frontopolar cortex	10/11	-18	57	3	-3.34	<0.001	918
R superior frontal gyrus/ frontopolar cortex	10	15	63	30	-3.55	<0.001	324
R anterior medial orbitofrontal cortex	11	3	72	-12	-3.40	<0.001	594
R precuneus	5/7	6	-54	66	-3.61	<0.001	3375
Cerebellar (vermis, 8)		0	-63	-30	-3.37	<0.001	1215
L supplementary motor area	6	-3	-15	63	-3.36	<0.001	1107
L inferior parietal lobule	40	-48	-45	54	-3.28	0.001	702
Affective Lability Scale (Total): [*Pre-Treatment scan*: (*Negative vs. Neutral*) × (*NoGo vs. Go*)]							
Positively correlated regions							
R hippocampus/ parahippocampal cortex	*20/28*	*18*	*-6*	*-18*	*2.89*	*0.002*	*378*
L hippocampus	*20*	*-21*	*-18*	*-9*	*2.93*	*0.002*	*648*
L inferior frontal gyrus (pars triangularis)	*45*	*-36*	*36*	*6*	*2.95*	*0.002*	*351*
L superior temporal gyrus	22	-54	-12	6	3.40	<0.001	1350
L middle temporal pole	37	-51	12	-27	4.05	<0.001	1593

L fusiform gyrus/ cerebellum	37	-33	-51	-24	4.38	<0.001	2187
R cerebellum 6		15	-60	-24	3.21	0.001	756
L postcentral gyrus/ precentral gyrus	4	-48	-6	33	3.36	<0.001	4158
R precentral gyrus	6	57	3	30	3.25	0.001	2619
L lingual gyrus	19	-27	-66	3	3.18	0.001	270
Negatively correlated regions							
L posterior medial orbitofrontal cortex/ ventral striatum	**11**	**-12**	**21**	**-9**	**-3.47**	**<0.001 (0.013*)**	**810**
R medial orbitofrontal cortex	*10*	*9*	*51*	*-3*	*-2.94*	*0.002*	*324*
R superior medial frontal cortex	9/32	12	42	39	-3.39	<0.001	405
R middle frontal gyrus/ dorsolateral prefrontal cortex	45	54	30	33	-3.41	<0.001	486
L posterior middle cingulate cortex	23	-15	-36	39	-3.50	<0.001	864
R posterior cingulate cortex	23	9	-45	36	-3.30	<0.001	3348
R supramarginal gyrus/ angular gyrus	40/39	51	-45	45	-4.22	<0.001	4509
R superior frontal gyrus/frontal eye fields	8	21	21	63	-3.38	<0.001	756
L precuneus	7	-6	-75	48	-3.34	<0.001	1728
Overt Aggression Scale (Aggression): [*Pre-Treatment scan*: (*Negative vs. Neutral*) × (*NoGo vs. Go*)]							
Positively correlated regions							
R gyrus rectus/ medial orbitofrontal cortex	11	9	39	-15	3.13	0.001	567
L gyrus rectus/ medial orbitofrontal cortex	*11*	*-12*	*39*	*-15*	*3.10*	*0.001*	*216*
R middle frontal gyrus/ dorsolateral prefrontal cortex	*46*	*27*	*54*	*21*	*3.34*	*<0.001*	*216*
R amygdala/ parahippocampal cortex	*34/28*	*21*	*-3*	*-18*	*2.64*	*0.004*	*81*
R inferior frontal gyrus (pars triangularis)	*45*	*57*	*36*	*-3*	*2.83*	*0.002*	*270*
L middle temporal gyrus	22	-57	-12	-9	3.16	0.001	1053
L middle temporal gyrus	22	-60	-54	21	3.40	<0.001	351
L fusiform gyrus	37	-42	-51	-18	3.97	<0.001	459
R precentral gyrus	6	57	6	21	3.19	0.001	1593
R cerebellum (vermis 4, 5)/ lingual gyrus	17/18	3	-48	6	4.26	<0.001	4104
L cerebellum		-18	-69	-33	3.62	<0.001	756
L cerebellum 6		-18	-54	-15	3.49	<0.001	324
L supramarginal gyrus	40	-66	-48	36	3.31	<0.001	1269
Negatively correlated regions							
L hippocampus	27	-15	-33	12	-3.15	0.001	6939
L angular gyrus	39	-54	-69	30	-4.17	<0.001	(above)
R anterior medial orbitofrontal cortex	10/11	12	57	-3	-3.16	0.001	945
R middle cingulate cortex/ posterior dorsal anterior cingulate cortex	23/24	12	-9	36	-3.74	<0.001	2619
R superior frontal gyrus/ frontal eye fields	8	18	18	66	-3.73	<0.001	837
L superior frontal gyrus/ frontal eye fields	8	-27	9	66	-3.48	<0.001	1701
R posterior middle temporal gyrus	20	60	-30	-9	-3.12	0.001	297
L precentral gyrus	6	-30	3	45	-4.12	<0.001	9639

Note: Initial voxel-wise p-value < 0.01 with a minimal spatial extent of cluster > ¼ cc; ***the peak voxel in an ROI at initial voxel-wise p < 0.001 and FWE corrected p<0.05**. Subthresholding trends in additional ROIs (the voxel-wise p-value at the peak voxel 0.001<p<0.01 and/or the cluster extent < ¼ cc) are listed in italic font, for the purpose of showing the direction/sign of the activations/correlations. L = left; R = right.


A
Emotional Linguistic Go/No-Go
run 1
run 2
run 3
run 4
NegGo
NeuGo
NegNoGo
PosGo
NeuNoGo
PosNoGo
16 Go trials ('abandon')
16 Go trials ('locate')
10 Go trials ('abandon') 6 NoGo trials ('pitiful')
16 Go trials ('support')
10 Go trials ('locate') 6 NoGo trials ('occupy')
10 Go trials ('support') 6 NoGo trials ('loyal')
B
NegGo
16 Go trials
NegNoGo
10 Go trials
6 NoGo trials
(36 s)
(1.5 s)
pitiful
(.75 s)
(1.5 s)
abandon
(1 s)
(19 s)
+
(36 s)
(1.5 s)
pitiful
(.75 s)
(1.5 s)
abandon
(1 s)
(19 s)
+