Journal of Psychiatric Research 81 (2016) 71–78

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Suicide attempters with Borderline Personality Disorder show differential orbitofrontal and parietal recruitment when reflecting on aversive memories

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ARTICLE INFO

Article history:
Received 29 October 2015
Received in revised form
10 May 2016
Accepted 24 June 2016

Keywords:
Borderline Personality Disorder
Emotion regulation
Neuroimaging
Suicide

ABSTRACT

Suicidal behavior and difficulty regulating emotions are hallmarks of Borderline Personality Disorder (BPD). This study examined neural links between emotion regulation and suicide risk in BPD. 60 individuals with BPD (all female, mean age = 28.9 years), 46 of whom had attempted suicide, completed a fMRI task involving recalling aversive personal memories. Distance trials assessed the ability to regulate emotion by recalling memories from a third-person, objective viewpoint. Immerse trials assessed emotional reactivity and involved recalling memories from a first-person perspective. Behaviorally, both groups reported less negative affect on Distance as compared to Immerse trials. Neurally, two sets of findings were obtained. The first reflected differences between attempters and non-attempters. When immersing and distancing, attempters showed elevated recruitment of lateral orbitofrontal cortex, a brain region implicated in using negative cues to guide behavior. When distancing, attempters showed diminished recruitment of the precuneus, a region implicated in memory recall and perspective taking. The second set of findings related to individual differences in regulation success – the degree to which individuals used distancing to reduce negative affect. Here, we observed that attempters who successfully regulated exhibited precuneus recruitment that was more similar to non-attempters. These data provide insight into mechanisms underlying suicide attempts in BPD. Future work may examine if these findings generalize to other diagnoses and also whether prior findings in BPD differ across attempters and non-attempters.

Suicide poses significant human and public health costs (Prevention, 2015). Although suicide attempts are common in many psychological disorders (Harris and Barraclough, 1997; Qin, 2011; Qin et al., 2003), it is particularly common in Borderline Personality Disorder (BPD) (Fertuck et al., 2007; Oldham, 2006), a serious mental illness characterized by interpersonal and affective instability. More than 60% of individuals with BPD attempt suicide and the rate of suicide completion in BPD is 400 times that of the general population (Kullgren et al., 1986; Qin, 2011). Yet, some individuals with BPD never attempt suicide, begging the question of what differentiates attempters and non-attempters.

Difficulties with emotion regulation underlie core BPD

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http://dx.doi.org/10.1016/j.jpsychires.2016.06.020

symptomology including affective instability and intense anger (Glenn and Klonsky, 2009; Yen et al., 2002). While prior research suggests that emotion dysregulation predicts suicide risk in BPD, the neural bases of suicide risk in BPD remain unknown. As such, the present study sought to answer three questions.

The first question was whether attempters and non-attempters differ *generally* in how they respond to emotional stimuli, both when responding reactively and when attempting to regulate their emotions. Structural neuroimaging studies in BPD (Soloff et al., 2012, 2014) and both structural and functional neuroimaging studies in depressed samples suggest that suicide attempters and non-attempters exhibit differences in brain regions implicated in emotional processing and decision making (Cox Lippard et al., 2014; Dombrovski et al., 2013; Du et al., 2014; Gujral et al., 2014; Leyton et al., 2006; Monkul et al., 2007; Oquendo et al., 2003; Pan et al., 2013; Poulter et al., 2010; Soloff et al., 2014; Soloff et al., 2012; Sublette et al., 2013). Neuroimaging and postmortem studies have linked suicidal behavior to functional and structural alterations in orbitofrontal cortex (Jollant et al., 2008; Leyton et al., 2006; Oquendo et al., 2003; Sublette et al., 2013), which is important for coordinating behaviors in accordance with prior experience, goals, and context (Roy et al., 2012; Rudebeck et al., 2013; Schoenbaum et al., 2011). Orbitofrontal dysfunction has also been linked to symptomology and suicide risk in BPD (Berlin et al., 2005; Soloff et al., 2014). Compared to healthy controls, individuals with BPD show exaggerated recruitment of lateral orbitofrontal regions involved in integrating sensory cues with information about punishments to guide behavior (Kringelbach and Rolls, 2004) when recalling aversive memories (Beblo et al., 2006; Driessen et al., 2004), interpreting eye gaze (Frick et al., 2012), and responding to provocation (New et al., 2009). As such, lateral orbitofrontal dysfunction may contribute to heightened emotionality in BPD. The present study examined whether suicide attempters with BPD show exaggerated lateral orbitofrontal recruitment compared to non-attempters when recalling emotional memories.

The second question was whether suicide attempters and non-attempters differ *specifically* in their ability to regulate emotion. To date, no neuroimaging studies have compared suicide attempters and non-attempters on a cognitive emotion regulation task, though prior work has shown that suicide attempters and non-attempters show structural differences in brain regions involved in visual and emotional processing such as occipital cortex and the insula, respectively (Soloff et al., 2012). Moreover, individuals with BPD exhibit atypical prefrontal, cingulate and subcortical response to affective cues relative to controls — though the nature of these differences varies widely across individuals (Ruocco et al., 2013; Schulze et al., 2015). Three studies have compared individuals with BPD to healthy controls when responding naturally to affective cues and when reappraising, which involves thinking about events differently so as to alter their emotional import and thus, regulate emotion. Although individuals with BPD report less negative affect when reappraising, they also show heightened amygdala responses and diminished activation in prefrontal, cingulate and/or occipitoparietal regions involved in emotion regulation and perspective taking relative to controls (Koenigsberg et al., 2009; Lang et al., 2012; Schulze et al., 2011). This suggests that individuals with BPD can reappraise but do so in a way that is mechanistically distinct from healthy individuals. Prior work suggests that mentalizing, or making sense of oneself or others by adopting different mental states, is enhanced or diminished in BPD, depending on the context (Fertuck et al., 2009), and that treating atypical mentalizing tendencies reduces the risk for suicidal behavior (Bateman and Fonagy, 2009). Given this and the fact that mentalizing is a component of effective self-regulation, it was expected that attempters and non-attempters might show different prefrontal, cingulate and occipitoparietal recruitment when reappraising memories.

The third question was whether individuals with BPD who are more successful at reappraising recruit prefrontal and occipitoparietal regions to a greater extent than individuals who are less successful and how this interacts with suicide behavior. Prior research indicates that healthy controls recruit prefrontal and occipitoparietal cortex to a greater extent than individuals with BPD (Koenigsberg et al., 2009; Lang et al., 2012; Schulze et al., 2011). Thus, the present study examined whether suicide risk might interact with regulation success to predict neural recruitment.

Despite clear links between suicide and difficulties with emotion regulation in BPD, no prior work has related the neural bases of emotion regulation to suicide in BPD. The present study sought to do so using a paradigm that assessed emotion regulation for upsetting memories wherein participants were instructed on a trial-by-trial basis to either emotionally immerse or distance (i.e., reappraise) themselves from their memories. Upsetting memories were used both because they effectively elicit negative affect and are clinically significant (Winter et al., 2014). Three hypotheses were tested. First, it was hypothesized that attempters would exhibit greater lateral orbitofrontal recruitment when reflecting on upsetting memories than non-attempters. Second, it was hypothesized that attempters would use different reappraisal tactics than non-attempters, as evidenced by different prefrontal and occipitoparietal recruitment, when distancing. Third, it was hypothesized that attempters who are more successful at reappraisal would show neural recruitment that is more similar to non-attempters in prefrontal regions and occipitoparietal regions implicated in self-regulation and mentalizing.

1. Methods

1.1. Participants

Sixty unmedicated females with BPD participated in this study (see Supplemental Materials and Table 1). The Institutional Review Boards at New York State Psychiatric Institute and Columbia University approved this research. This manuscript describes all measures, conditions, and data exclusions relevant to these neuroimaging data.

Participants were recruited for a larger treatment study on BPD. As is common for treatment-seeking individuals with BPD, the majority of participants had a history of suicidal behavior. Sample size was based on the results of the treatment study power analysis, which did not stipulate how many attempters and non-attempters participated, and participant availability. The present data were collected prior to treatment assignment. Participants were recruited through psychiatrist and therapist referrals, advocacy group referrals, self-referrals, and advertisements. Exclusion criteria included being male and present organic mental syndromes. Participants were excluded from participation if they were unable to provide consent, had past or present bipolar I disorder, psychotic disorder, schizophrenic disorder, or any condition contraindicated for neuroimaging.

Forty-six patients had previously attempted suicide while 14 had not — rates that are consistent with the broader BPD population. All patients met DSM-IV criteria for BPD, as determined by the Structured Clinical Interview (SCID) for DSM-IV, parts I and II (Assocation, 2000).

1.2. Experimental design

1.2.1. Memory collection

In a pre-scanning testing session, a clinician asked participants

Table 1
Demographic characteristics of study participants.

	Attempter (n = 46)		Non-Attempter (n = 14)		Statistical analysis		
	Mean	*SD*	*Mean*	*SD*	*t*	*df*	*p*
Age	28.98	9.81	26.71	5.00	0.83	58	0.41
Affective lability scales	97.86	27.24	86.14	34.70	1.13	54	0.20
Barratt impulsivity scale	66.24	18.74	70.14	17.73	−0.69	57	0.49
Beck depression inventory	29.60	10.91	24.85	9.83	1.41	56	0.16
Brown-goodwin aggression history scale	20.20	5.21	18.50	4.04	1.12	58	0.27
Buss-durkee hostility inventory	48.37	10.53	44.57	10.83	1.17	55	0.25
DERS	127.19	22.3	130.1	21.9	−0.43	55	0.67
Global assessment of functioning	49.04	6.78	52.93	6.59	−1.89	57	0.07
Hamilton anxiety rating scale	14.70	6.04	15.64	4.85	−0.54	58	0.59
Hamilton depression rating scale	26.39	9.66	22.79	9.85	1.22	58	0.23
Lifetime number of suicide attempts	2.15	1.3	0	–	6.01	58	<0.001*
Scale for suicidal ideation	9.80	9.19	4.07	4.55	2.24	58	0.03*
Zanarini scale for BPD	16.35	6.06	13.79	4.00	1.48	58	0.14
	n	*%*	*n*	*%*	X^2	*df*	*p*
Female	46/46	100	14/14	100	–	–	–
White	28/46	60.9	7/14	50	0.52	1	0.47
High school graduate or above	44/46	95.7	14/14	100	0.63	1	0.43
Single (includes separated and divorced)	36/46	78.3	12/14	85.7	0.37	1	54
Currently employed	27/46	58.7	11/14	78.6	1.83	1	0.18
History of psychiatric hospitalization	34/46	73.9	9/14	64.3	0.49	1	0.48
Current MDE	36/46	78.3	7/14	50	4.22	1	0.04*
Lifetime MDD	42/46	91.3	11/14	78.6	1.69	1	0.19
Current PTSD	12/46	26.1	1/14	7.1	2.27	1	0.13

Suicide attempters and non-attempters did not differ significantly on demographic variables. Attempters were more likely to be in a current depressive episode than non-attempters; however, they did not differ significantly with regard to lifetime history of major depressive disorder. Significant correlations (p < 0.05) are denoted with a "*".

to recall 8 upsetting memories from the last 6 months of their lives that made them feel sad, mad or upset. If participants had difficulty, they were told that upsetting situations with family, friends and work are often sources of distress for people and if necessary, were asked to recall memories involving feeling ashamed, humiliated, rejected, misunderstood or hopeless. Participants rated each memory on a scale of 1–10 in terms of how initially distressing it was and its current intensity and vividness (all task memories were rated as a 7 or higher). The clinician and participant created brief phrases to be used as memory cues for the fMRI task. Participants provided 4 neutral memories for training purposes. Before scanning, participants were tested to ensure that memories were still emotionally evocative (Mean negative affect rating on scale of 1–5 = 3.72, S.D. = 0.77) and recallable (Mean vividness rating on scale of 1–5 = 4.10, S.D. = 0.81). Pre-scanning ratings of negative affect ($t(51) = 0.91$, $p = 0.37$) and vividness ($t(51) = 0.74$, $p = 0.47$) did not differ significantly between the attempters and non-attempters (ratings were not recorded for 3 non-attempters and 4 attempters).

1.2.2. Task training

On 'immerse' trials, participants were told to see the situation in the first person and to feel any emotions that may arise. On 'distance' trials, participants were told to watch their memory unfold from a distance and to adopt the perspective of a reporter who is focused on the facts of their memory rather than its emotional details. Participants practiced the strategies with neutral memories so they did not habituate to upsetting memories. Participants practiced distancing and immersing two memories aloud with an experimenter before practicing silently with two additional memories. All participants successfully described the strategy to the experimenter and verbalized how to distance themselves.

Suicide history information was obtained using the Columbia Suicide History Form (CSHF) (Salvador et al., 2016). The CSHF asks individuals about intent associated with each behavior and only self-injurious acts with intent to die are classified as suicide attempts. Among attempters, the mean number of suicide attempts was 2.15 (S.D. = 1.33, range 1–6), mean number of days since last attempt was 1522.84 (S.D. = 2142.84, range 15–9774 days), and for the most serious suicide attempt, intent was 14.57 (S.D. = 4.85, range 5–22) and lethality was 2.43 (S.D. 1.31, range 0–6). Suicidal ideation was 7.63 (S.D. = 6.39, range 0–25) for attempters and 4.50 (S.D. = 4.26, range 0–12) for non-attempters. More attempters had comorbid depression, as determined by the SCID, than non-attempters (X^2 (1, N = 60) = 4.22, $p < 0.05$).

1.2.3. fMRI task

Participants completed four fMRI task runs, each comprised of four trials (Fig. 1a). Each trial began with a memory cue (10 s) that prompted participants to recall the memory indicated. After a brief delay, the memory cue was presented with an instructional cue ('immerse' or 'distance') for 20 s, during which time participants either immersed or distanced themselves from their memory. Participants then rated their negative affect and the vividness of the memory recalled on a scale of 1–5. Trial-by-trial self-report is routinely used to evaluate regulatory success in healthy and clinical populations in the reappraisal literature (e.g., Koenigsberg et al., 2009; Ochsner et al., 2002) because moment-to-moment self-report is a more accurate means of assessing emotions than retrospective report (Stone and Shiffman, 1994) – particularly among individuals with BPD who may have memory distortions (Winter et al., 2014). After each trial, participants completed an active baseline task involving making button presses to indicate the direction of an arrow for 20 s (Stark and Squire, 2001).

Participants recalled two memories twice per run, once with the immerse instruction and once with the distance instruction. Half of memories were presented with the immerse instruction first and half were presented with the distance instruction first. Stimuli were displayed using an LCD projector and a back-projection screen. Participants responded using a five-finger-button-response (Avotec Inc. and Resonance Technologies).

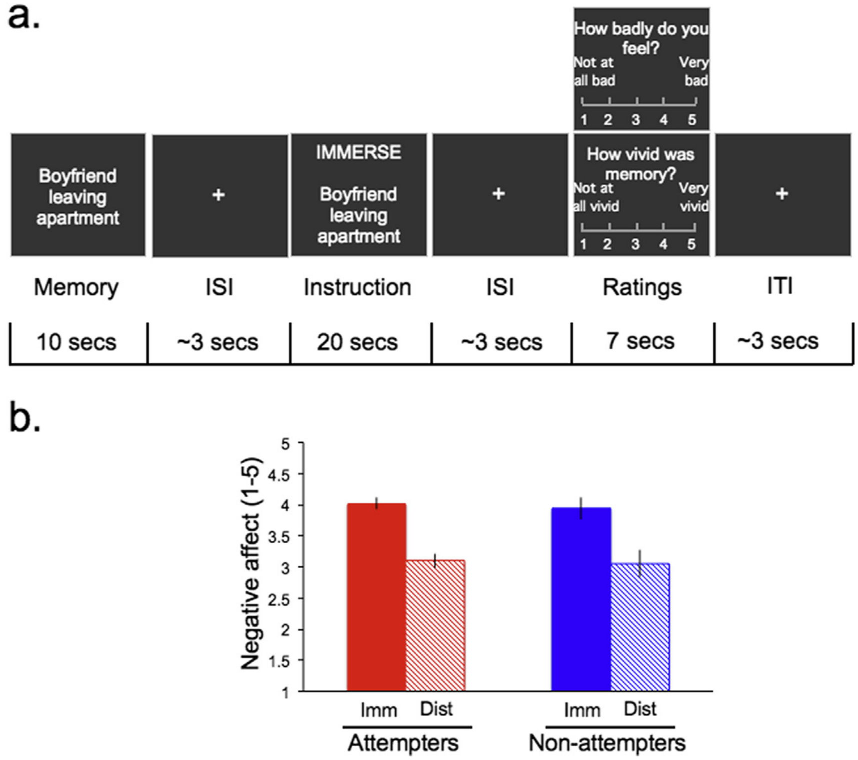

Fig. 1. (**a**) Trial structure for the reappraisal of aversive memories task. (**b**) Self-reported negative affect as a function of strategy and suicide risk group, error bars represent standard error. A significant effect of strategy was observed such that participants reported less negative affect when reappraising on Distance trials than on Immerse trials, $F(1,58) = 99.02$, $p < .001$. No significant effects of group were observed nor did group significantly interact with strategy (p's > 0.34).

1.3. fMRI acquisition

Whole-brain data were acquired on a GE 1.5 T scanner (General Electric, Milwaukee, Wisconsin). Functional data were acquired with a T2*-sensitive EPI sequence (28 4 mm contiguous axial slices, TR = 2000 ms, TE = 34 ms, flip angle = 84°, FOV = 22.4 cm) Anatomical images were acquired with a T1-weighted SPGR scan (124 1.5 mm slices, TR = 19 ms, TE = 5 ms, FOV = 22 cm).

1.4. Behavioral data analysis

Self-reported negative affect and memory vividness were analyzed using SPSS 19.0. For both variables, a repeated-measures ANOVA was used to assess the effects of strategy (within-subjects: immerse, distance) and suicide attempt history (between-subjects: attempters, non-attempters).

1.5. fMRI preprocessing and subject-level analyses

1.5.1. Preprocessing

The first four volumes of each functional scan were discarded to avoid saturation effects. Preprocessing was conducted using statistical parametric mapping software (SPM8, Wellcome Department of Cognitive Neurology, London, UK) in NeuroElf (http://neuroelf.net). Preprocessing included slice time correction, realignment, and co registration of the functional and structural data. Coregistered anatomical images were segmented into gray and white matter and normalized to the standard MNI template brain and warping parameters were applied to all functional images. Normalized functional images were resliced to 3 × 3 × 3 mm voxels and spatially smoothed with a 6-mm Gaussian filter. Volumes containing more than 1.5 mm (translation) or 2° (rotation) frame-to-frame motion were censored (mean volumes removed = 0.62, SD = 1.47).

1.5.2. First-level fMRI analyses

Robust regression analyses were performed on the conditions of interest in NeuroElf for each participant. Memory cue, strategy cue (separate regressors were made for the immerse and distance conditions), rating period and active baseline portions of each trial were modeled as boxcar regressors convolved with a canonical hemodynamic response function. Motion parameters and high-pass temporal filter parameters were included as nuisance regressors. All analyses focused on the first 10-s portion of the strategy period, as this was when regulation was thought to be most strongly engaged.

1.6. Group-level fMRI analyses

Group data were analyzed using a random-effects analysis. Data were constrained by a gray-matter mask based on the MNI-standardized Colin-brain (67,407 3 mm voxels) and were initially thresholded at $p < 0.005$, uncorrected. Smoothness estimates were calculated in NeuroElf separately for each contrast and ranged from 8.4 to 13.7 mm (smoothness estimates can differ for t-tests versus correlations with independent behavioral variables, in part because behavioral variables may be noisy and are applied to all voxels uniformly). Smoothness estimates and the gray matter mask size were inputted into AFNI's 3dClustSim so as to calculate cluster extent thresholds (54–136 voxels) that held the family-wise error rate at alpha <0.05.

An *a priori* region-of-interest in lateral orbitofrontal cortex was defined by combining the bilateral inferior and middle orbital AAL region of interests available in the MarsBaR toolbox for SPM8.

Clusters falling within this 5325 voxel mask are reported if they achieved $p < 0.05$, small volume corrected ($p < 0.005$, uncorrected; 29 voxels).

1.6.1. Group analyses examining memory recall

To examine memory recall, the initial memory retrieval period was contrasted against active baseline.

1.6.2. Group analyses examining regulatory strategy

Task effects were examined in two steps. First, the immerse and distance conditions were collapsed and compared to active baseline. Second, distance and immerse trials were compared.

1.6.3. Group analyses examining suicide history

Group differences (attempters > non-attempters) were examined for the immerse + distance > active baseline (main effect of group) and distance > immerse (group × regulation interaction) contrasts.

1.6.4. Analyses examining regulation success

To examine what neural processes supported effective reappraisal, a regulation success score – the percent decrease in negative affect observed on distance as compared to immerse trials – was calculated for each participant. These scores were correlated with the distance > immerse contrast (see Supplemental Materials). Beta values were extracted from brain regions showing differential responses for attempters and non-attempters and were probed using a repeated-measures ANOVA in SPSS.

1.6.5. Group analyses examining clinically-relevant symptomology

Neural correlates of individual differences on the Hamilton Depression Inventory and Difficulties with Emotion Regulation Scale (DERS) are reported in the Supplemental Materials. Given that more attempters were clinically depressed than non-attempters, analyses controlling for depression status were conducted on all brain regions showing group differences (see Supplementary Materials).

1.6.6. Analyses examining number of suicide attempts and days since last attempt

Within the attempter group, number of prior suicide attempts and days since last attempt were correlated with the immerse + distance > active baseline and distance > immerse contrasts (see Supplemental Materials).

2. Results

2.1. Behavioral results

Participants reported less negative affect (Mean difference = 0.91, $F(1,58) = 99.02$, $p < .001$) and less vivid memories (Mean difference = 0.26, $F(1,58) = 23.29$, $p < .001$) on distance than immerse trials (Fig. 1b). No effect of group was observed nor did group interact with strategy (p's > 0.34). Regulation success – the percent decrease in negative affect observed on distance versus immerse trials – did not differ between attempters and non-attempters ($Mean_{attempters} = 22.89\%$; $Mean_{non\text{-}attempters} = 23.48\%$; $t(58) = 0.14$, $p = 0.89$).

2.2. fMRI results

2.2.1. Group analyses examining memory recall

Across the entire sample, recalling memories (prior to immersing or distancing) recruited lateral prefrontal, temporal (including the hippocampus and amygdala) and occipital cortex (ST1). Attempters recruited the thalamus more than non-attempters while non-attempters recruited occipital cortex more than attempters during memory recall.

2.2.2. Analyses examining regulatory strategy

Relative to active baseline, distancing and immersing recruited dorsal and lateral prefrontal cortex, hippocampus, and occipital and parietal cortex (ST2). The two conditions also differed from one another, such that immersing was associated with greater recruitment of bilateral dorsolateral and parietal cortices and right temporal cortex, while distancing was associated with greater activation of the hippocampus and brainstem (ST2). Masking the distance > immerse contrast with clusters from the distance + immerse > active baseline contrast revealed similar, albeit slightly smaller, clusters.

2.2.3. Group analyses examining suicide history

Suicide attempters showed both general (i.e., in both conditions) and specific (i.e., in the distance but not immerse condition) differences from non-attempters.

Generally, suicide attempters recruited lateral orbitofrontal cortex to a greater extent than non-attempters (i.e., immerse + distance > active baseline; Table 2; Fig. 2a). Exploratory analyses revealed that attempters showed greater recruitment of left lateral OFC for immerse > active baseline (MNI coordinates: -36, 45, -15; 30 voxels) and distance > active baseline (MNI coordinates: -33, 39, -9; 16 voxels) at $p < 0.005$, uncorrected.

Specifically, attempters showed less recruitment of the precuneus and cuneus relative to non-attempters when distancing versus immersing themselves from their emotional memories (Table 2; Fig. 2b).

2.2.4. Analyses examining regulation success

Suicide group and regulation success did not significantly interact to predict beta values extracted from the precuneus/cuneus cluster identified in the contrast comparing attempters and non-attempters during reappraisal ($F(1,56) = 2.99$, $p = 0.089$; Fig. 2b). For exploratory and descriptive purposes, correlations between regulation success and precuneus/cuneus beta values were performed within each group. Regulation success predicted greater precuneus/cuneus recruitment for attempters ($r = 0.41$, $p = 0.005$) but not non-attempters ($r = -0.19$, $p = 0.53$). A follow-up moderation analysis using the Johnson-Neyman technique revealed that for individuals with regulation success scores of 30.69% or above (roughly the top quartile of all participants), the effect of group on precuneus/cuneus was non-significant. These results provide preliminary evidence that precuneus/cuneus activation was

Table 2
Brain regions showing differential recruitment during distancing and immersing for attempters and non-attempters.

Region	Side	# Voxels	t	Coordinates		
				x	*y*	*z*
Distance + Immerse > active baseline, Attempters > non-attempters						
*Lateral orbitofrontal cortex	L	37	3.77	−33	39	−9
Distance + Immerse > active baseline, Non-attempters > Attempters						
Occipital gyri	L	72	4.23	−36	−96	6
Occipital gyri, cuneus	R	231	6.62	39	−90	−6
Distance > immerse, Non-attempters > attempters						
Cuneus; precuneus	R	65	4.27	18	−75	24
Distance > immerse, Attempters > non-attempters						
No regions identified						

t = maximum t statistic for a given cluster. For side, R = right, L = left, M = medial.
*Identified within lateral orbitofrontal cortex mask and evaluated at $p < 0.005$, 29 voxels.

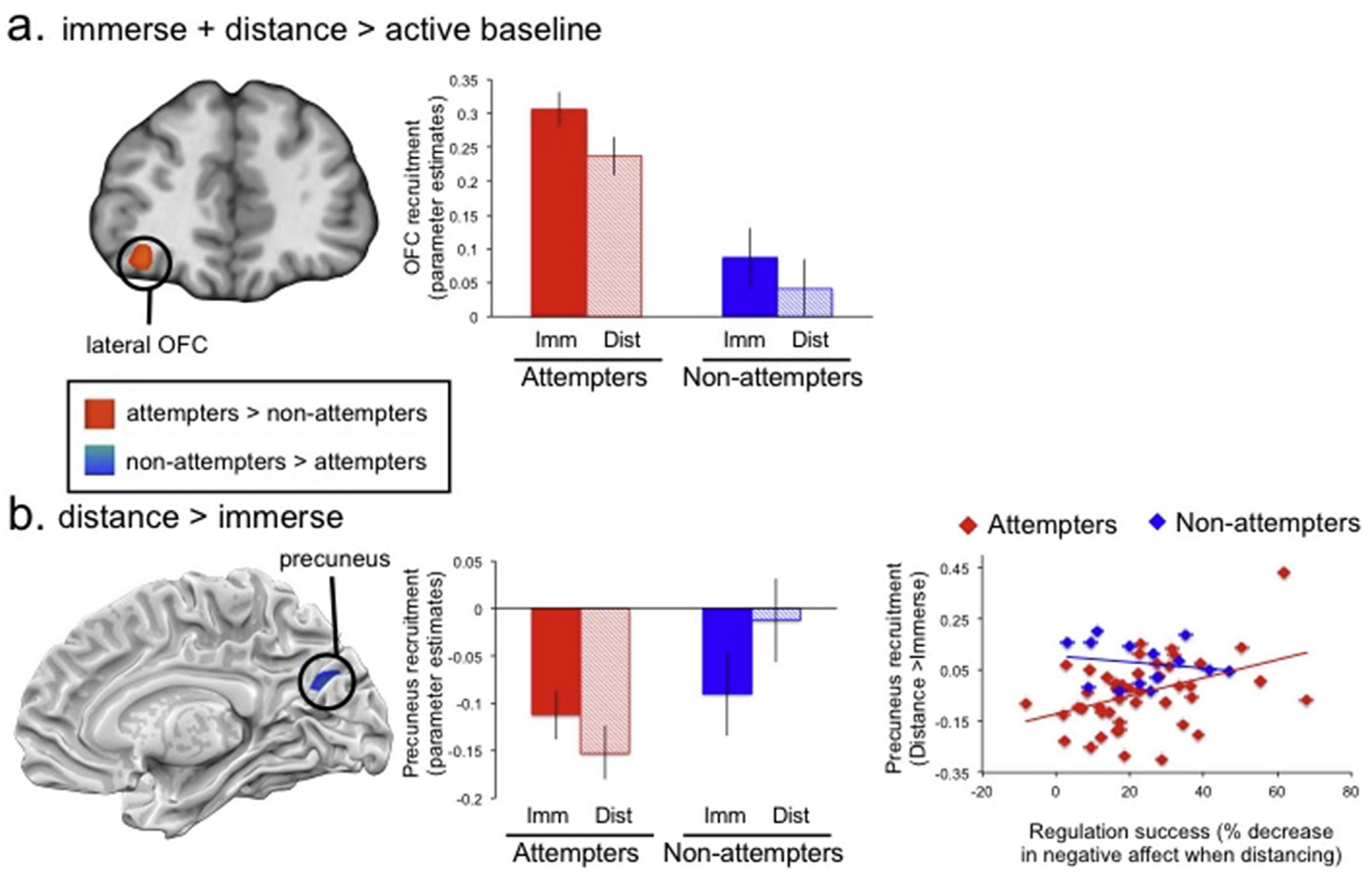

Fig. 2. (**a**) Compared to non-attempters, attempters showed enhanced lateral orbitofrontal cortex recruitment both when immersing and distancing relative to active baseline, $p < 0.05$, small volume corrected. (**b**) **Left**: Non-attempters recruited the cuneus and precuneus more strongly than attempters when reappraising (distance > immerse), $p < 0.05$, family-wise error corrected. **Right**: Reappraisal success significantly predicted cuneus/precuneus recruitment for attempters but not non-attempters.

comparable between non-attempters and attempters who were highly effective regulators.

3. Discussion

The present study used a novel paradigm to examine the neural bases of suicide in BPD. While both groups recruited prefrontal, subcortical, and occipitotemporal regions during memory retrieval – consistent with prior work in healthy adults (Svoboda et al., 2006) – they also differed from each other in three key ways. First, compared with non-attempters, attempters recruited lateral orbitofrontal cortex – a brain region implicated in suicide and BPD – both when immersing and distancing. This result, together with the fact that the number of days since last suicide attempt was not predictive of variability in brain or behavior measures of emotion regulation, suggest that suicide attempt history may function as a traitlike variable among individuals with BPD. Second, although attempters and non-attempters reported comparable reductions in negative affect when distancing, attempters recruited the precuneus and cuneus which are involved in attentional control, perspective taking and memory retrieval to a lesser degree than non-attempters (Spreng et al., 2009). Third, among attempters, those who were more successful at reappraising showed precuneus/cuneus activation that was similar to non-attempters when distancing versus immersing. These findings have implications for how emotion regulation confers suicide risk in BPD.

3.1. Emotion regulation and suicide in BPD

The present study enhances our basic understanding of how emotion regulation relates to suicide risk in three ways.

First, self-report data suggest that both suicide attempters and non-attempters with BPD are capable of reappraising upsetting memories. While prior work has not compared reappraisal in attempters and non-attempters, this result is consistent with clinical work demonstrating that therapies that teach cognitive regulatory strategies are effective in treating BPD (Bateman and Fonagy, 2004; Levy et al., 2006; Lynch et al., 2007; Yeomans et al., 2013), and also experimental work suggesting that individuals with BPD can reappraise aversive photographic images (Koenigsberg et al., 2009; Lang et al., 2012; Schulze et al., 2011).

Second, the fact that attempters showed stronger lateral orbitofrontal recruitment relative to non-attempters builds on prior work implicating orbitofrontal dysfunction in suicide (Jollant et al., 2008; Leyton et al., 2006; Monkul et al., 2007; Oquendo et al., 2003) and BPD (Driessen et al., 2004; Kamphausen et al., 2013; Silbersweig et al., 2007). In healthy individuals, lateral orbitofrontal recruitment signals the need to change behavior in accordance with punishment or changing contingencies (Kringelbach and Rolls, 2004). Thus, exaggerated lateral orbitofrontal recruitment in attempters may reflect compensatory efforts to recall or manipulate emotional memories. Alternatively, it is possible that group differences in orbitofrontal function could reflect underlying anatomical differences (Drevets et al., 1997), which ought to be explored in future studies.

Third, it is striking that although attempters and non-attempters had comparable regulation success and DERS scores, they showed different neural activation. These results suggest that attempters approach regulatory challenges differently, but equally successfully, as non-attempters. An alternative explanation would be that attempters and non-attempters employed different variants of reappraisal or that one group reappraised while the other group did not. However, given that the groups received identical training and exhibited comparable regulation success, this seems unlikely. Prior work has implicated BPD with reduced reappraisal-related cuneus and precuneus recruitment (Lang et al., 2012; Schulze et al., 2011), while in the present study attempters showed reduced recruitment of such regions relative to non-attempters. Given the role of the precuneus and cuneus in mental imagery (Ganis et al., 2004), autobiographical memory retrieval (Spreng et al., 2009), and computations involving distance, perspective, and space (Kravitz et al., 2011), this finding dovetails with a broader literature linking suicide to atypical memory processes (Richard-Devantoy et al., 2014), and suggests that attempters are less able to recall upsetting memories from a distanced perspective than non-attempters. Thus, therapies that target patients' ability to view events from different perspectives such as Mentalization-Based Therapy (Bateman and Fonagy, 2009) and Transference-Focused Psychotherapy (Levy et al., 2006) may be particularly helpful for attempters.

With these points in mind, it is important to consider whether attempters might differ from non-attempters not only in how they regulate negative emotion but also in terms of other risk factors that predict suicide risk. Prior work suggests that comorbid BPD and depression predicts greater suicide risk, perhaps because of a two-prong hit to self-regulatory systems and stronger negative mood (Oldham, 2006). For this reason, it is somewhat surprising that brain activation that differed between attempters and non-attempters was unrelated to depression. It is also possible that attempters struggle more than non-attempters with emotion regulatory challenges that were not assessed in the present paradigm but nonetheless confer suicide risk. For example, substance use is a significant risk factor for suicide in BPD (Oldham, 2006), suggesting perhaps that attempters struggle to regulate both positive (i.e., substance craving) and negative emotions while non-attempters struggle exclusively with regulating negative emotion. As such, future work could examine whether attempters show more global self-regulatory problems than non-attempters.

3.2. Individual differences in BPD

The present results highlight the significance of individual differences in BPD in two ways. First, they suggest that main effect analyses may provide an incomplete characterization of BPD. For example, distancing was associated with reduced prefrontal recruitment during reappraisal at the group level but the opposite was true for individuals who were successful at reappraising (Supplemental Materials). Second, the present results corroborate clinical research suggesting that individual differences in emotion regulation predict suicide risk in BPD (Yen et al., 2004). Specifically, among attempters, those who were highly successful at reappraising showed brain activity that was more similar to non-attempters. Future work may seek to examine whether such individual differences predict treatment response or future suicide attempts.

3.3. Limitations

Three limitations ought to be noted alongside these findings. First, consistent with the suicide literature (Soloff et al., 1994), attempters had a higher rate of comorbid depression than non-attempters. However, depression did not predict activation in brain regions showing group effects. Second, the non-attempter group was smaller than the attempter group. However, similar group effects were observed when sample sizes were matched, albeit at more relaxed statistical thresholds (Supplemental Materials). Because participants did not vary widely in their number of prior suicide attempts, future work ought to examine the significance of number of attempts in a larger sample. Finally, neuroimaging data were acquired on a 1.5 T magnet, which has a lower signal-to-noise ratio than higher Tesla magnets (Krasnow et al., 2003).

Author contribution

JAS, EF, HK, KNO and BS designed the study. JAS, ADH, SC, EB, JS, MFG, EF, HK, AC-W, BSB and MC collected the data. JAS, ADH, SC, JS and JW analyzed the data. JAS, SC, KNO and BS wrote the manuscript. All authors approved a final version of this manuscript.

Funding source

Completion of this article was supported by grants MH094056 (Silvers), MH061017 (Stanley), MH090964 (Mann), AG043463 (Ochsner) and HD069178 (Ochsner). Although NIH provided the funding for the study, the sponsoring agency had no further role in the study design, planning, data collection, analysis and interpretation of data, and writing of the report or decision to submit the manuscript for publication.

Conflicts of interest

None.

Acknowledgements

Completion of this article was supported by grants MH094056 (Silvers), MH061017 (Stanley), MH090964 (Mann), AG043463 (Ochsner) and HD069178 (Ochsner).

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2016.06.020.

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