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

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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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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