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Structural Brain Abnormalities and Suicidal Behavior in Borderline Personality Disorder

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Abstract

Background—Structural brain abnormalities have been demonstrated in subjects with BPD in prefrontal and fronto-limbic regions involved in the regulation of emotion and impulsive behavior, executive cognitive function and episodic memory. Impairment in these cognitive functions is associated with increased vulnerability to suicidal behavior. We compared BPD suicide attempters and non-attempters, high and low lethality attempters to healthy controls to identify neural circuits associated with suicidal behavior in BPD.

Methods—Structural MRI scans were obtained on 68 BPD subjects (16 male, 52 female), defined by IPDE and DIB/R criteria, and 52 healthy controls (HC: 28 male, 24 female). Groups were compared by diagnosis, attempt status, and attempt lethality. ROIs were defined for areas reported to have structural or metabolic abnormalities in BPD, and included: mid-inf. orbitofrontal cortex, mid-sup temporal cortex, anterior cingulate, insula, hippocampus, amygdala, fusiform, lingual and parahippocampal gyri. Data were analyzed using optimized voxel-based morphometry implemented with DARTEL in SPM5, co-varied for age and gender, corrected for cluster extent (p<.001).

Results—Compared to HC, BPD attempters had significantly diminished gray matter concentrations in 8 of 9 ROIs, non-attempters in 5 of 9 ROIs. Within the BPD sample, attempters had diminished gray matter in Lt. insula compared to non-attempters. High lethality attempters had significant decreases in Rt. mid-sup. temporal gyrus, Rt. mid-inf. orbitofrontal gyrus, Rt. insular cortex, Lt. fusiform gyrus, Lt. lingual gyrus and Rt. parahippocampal gyrus compared to low lethality attempters.

Conclusions—Specific structural abnormalities discriminate BPD attempters from non-attempters and high from low lethality attempters.

Objectives of the Study

Suicidal behavior is associated with abnormalities in regulation of emotion, impulsivity, executive cognitive function, and episodic memory. Attempters appear more sensitive to social disapproval, make more high risk decisions, and have reduced ability to envision

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positive outcomes based on current memory (Van Heeringen et al., 2011; Jollant et al., 2005). High lethality attempters have deficits in executive cognitive functions independent of deficits associated with co-morbid depression (Keilp et al., 2001). Structural and metabolic abnormalities in areas which mediate these psychological functions may contribute a neurobiologic diathesis to suicidal behavior at times of stress, independent of diagnoses (Mann, 2003).

There is a surprising paucity of imaging studies directly contrasting suicide attempters and non-attempters, or correlating imaging results with suicidal behavior. MRI studies of suicide attempters with major depression describe diminished brain volumes in very diverse areas of grey and white matter, including: the orbital frontal cortex, basal ganglia, cingulate cortex, insular cortex, amygdala, parahippocampus and hippocampus (Van Heeringen et al., 2011; Monkul et al., 2007; Ahearn et al., 2001; Hwang et al., 2010). PET studies demonstrate diminished metabolism in ventromedial and lateral areas of prefrontal cortex in high lethality depressed attempters. (Oquendo et al., 2003). Among schizophrenic patients, attempters have diminished grey matter density in left orbital frontal and left superior temporal lobe compared to non-attempters (Aguilar et al., 2008). Given the diversity in risk factors for suicide, it is not surprising that the neurobiologic mediation of suicidal behavior would involve multiple brain regions, or differ across diagnoses. In this study, we investigated structural brain differences between suicide attempters and non-attempters, high and low lethality attempters with Borderline Personality Disorder (BPD).

Why study suicidal behavior in BPD?

Recurrent suicidal behavior is a diagnostic criterion for BPD, a highly prevalent disorder found in approximately 1% of the population (Paris, J. 2010, for review). As a group, BPD patients are characterized by a high incidence of suicide attempts (over 70%), a high frequency of attempts within individuals (on average 3 lifetime attempts), and a suicide completion rate of 3–10% (Soloff et al., 2000, Paris & Zweig-Frank, 2001). Impulsive aggression and emotion dysregulation, risk factors for suicidal behavior across diagnoses, are defining characteristics of this disorder. Impairment in executive cognitive function and episodic memory have been demonstrated in neuropsychological studies in BPD (Fertuck et al., 2006; Ruocco, 2005). These deficits are associated with increased vulnerability to suicidal behavior at times of emotional stress.

Imaging Studies in BPD

MRI studies in BPD subjects compared to healthy controls report volume loss and diminished grey matter concentrations in areas of the frontal lobes, including orbital frontal cortex, and anterior cingulate cortex, in areas of the medial temporal lobes, including hippocampus, and amygdala (Van Heeringen et al., 2011; Schmahl & Bremner, 2006; Lyoo et al., 1998; Tebartz van Elst et al., 2003; Rusch et al., 2003; Hazlett et al., 2005; Zetzsche et al., 2007). Using the techniques of voxel-based morphometry (VBM) described in this study, we previously reported significant bilateral reductions in grey matter concentrations in BPD subjects compared to healthy controls in anterior cingulate cortex and regions of the medial temporal lobe, including the hippocampus, amygdala, parahippocampal gyrus and uncus (Soloff et al., 2008).

PET studies in subjects with BPD report decreased metabolic function in areas of prefrontal cortex, including orbital frontal and ventromedial cortex, in cingulate gyrus, and in temporal cortex (Schmahl & Bremner, 2006). In impulsive female subjects with BPD (and no MDE), we found prefrontal hypometabolism, centered in medial orbital cortex bilaterally (BA 9, 10, 11) relative to healthy controls (Soloff et al., 2003). These structures are part of a fronto-

limbic network involved in emotion regulation, cognitive and behavioral control, and overlap areas of reported structural abnormality in BPD.

PET studies have also demonstrated diminished metabolic responses to serotonergic challenge in patients with BPD (and other impulsive PDs), using d,l fenfluramine (FEN), or meta-chlorophenylpiperazine (m-CPP). Following challenge with FEN or m-CPP, subjects with BPD (and other impulsive PDs) demonstrate blunted cortical metabolic responses relative to healthy controls in orbital frontal, adjacent ventromedial, and cingulate cortex. Blunted central serotonergic response to FEN or m-CPP is associated with impulsive aggression and suicidal behavior in BPD and other disorders (Siever et al., 1999; Soloff et al., 2000b; New et al., 2002; Soloff et al., 2005). These imaging studies complement earlier post-mortem receptor studies of suicide victims which found evidence of diminished central serotonergic function independent of diagnosis in ventral lateral and orbital frontal cortex. (Arango et al., 1995; Arango et al., 1997; Mann & Stoff, 1997).

No prior imaging study has selected BPD subjects for histories of suicide attempts, or related structural findings to suicidal behavior. Using voxel-based morphometry (VBM), we compared BPD attempters, non-attempters, and control subjects, choosing regions of interest (ROIs) previously associated with structural and metabolic abnormalities.

Materials and Methods

Subjects for this study were participants in a longitudinal study of suicidal behavior in BPD, approved by the Institutional Review Board of the University of Pittsburgh, and funded by the NIMH. They were recruited by advertisement from the outpatient programs of the Western Psychiatric Institute and Clinic, and surrounding community. All subjects gave written informed consent for participation.

Diagnoses were determined by Master's prepared research raters using structured interviews. Axis I disorders were diagnosed using the Structured Clinical Interview for DSM III-R (DSM IV was added when it became available) (Spitzer et al., 1998; First et al., 2005). Axis II was diagnosed using the International Personality Disorders Examination (IPDE), which has a lifetime framework (Loranger et al., 1997). The Diagnostic Interview for Borderlines (DIB) (Gunderson et al., 1981) was administered as an independent measure of diagnosis and recent symptom severity, with a timeframe of 3 months to 2 years for individual subscales. (The DIB was used to preserve continuity with the longitudinal study; however, the Diagnostic Interview for Borderlines-Revised (DIB-R) was added and used concurrently when it became available (Zanarini et al., 1989). For inclusion, participants had to meet diagnostic criteria for BPD on the IPDE (probable or definite), have a score of 7 or more (definite) on the DIB, and 8 or more (definite) on the DIB-R. Exclusion criteria included any past or current Axis I diagnosis of schizophrenia, delusional (paranoid) disorder, schizo affective disorder, bipolar disorder, or psychotic depression. Subjects were also excluded for physical disorders of known psychiatric consequence (e.g., hypothyroidism, seizure disorder, or brain injury), and borderline mental retardation. Medical records were reviewed where available to confirm inclusion and exclusion criteria. Final diagnoses were determined by consensus of raters using all available data. Control subjects were free of all Axis I and II disorders. Attempter status and medical lethality of attempts were obtained by interview using the Columbia Suicide History Form and Lethality Rating Scale (Oquendo et al., 2003). Scans were obtained from newly recruited subjects and from subjects already enrolled in the longitudinal study at time of their annual follow-up assessment. As a result, all subjects had updated SCID interviews for current diagnoses within 2 weeks of the scan. A current Global Assessment Scale score (GAS) and 24 item Hamilton Rating Scale for Depression (HamD-24) (Guy, 1976), were also obtained prior to

the MRI scan. Lethality status (High vs. Low) was determined by a median split of lifetime maximum Lethality Rating Scale scores among all attempters. High lethality status was defined as having a lifetime maximum score of 4 or greater. (e.g. For a suicide attempt by overdose with sedative drugs, a score of 4 is defined as "comatose; injury sufficient for hospitalization.")

All subjects were physically healthy, free of drugs of abuse and alcohol for at least one week prior to the scan. Psychotropic medication use was noted and compared between groups (below). Female subjects were required to have a negative screen for pregnancy, and all subjects a negative urine toxicology screen for drugs of abuse immediately prior to the scan. Some BPD subjects were taking psychoactive medication.

Subject Characteristics

Demographic, diagnostic and clinical characteristics of the samples are presented in Table 1. Co-morbidity on Axis I was determined for all SCID diagnoses, for current and lifetime diagnoses; however, only Major Depressive Disorder (MDD), Alcohol Use Disorder (AUD), and Post-Traumatic Stress Disorder (PTSD) were of sufficient frequency or clinical interest to be reported here. There were 68 BPD subjects compared to 52 healthy controls (HC), with no significant differences between groups in age or race. As expected, BPD subjects were disproportionately female, had significantly lower SES, more depressed mood (HamD), lower global functioning (GAS), and more histories of childhood physical and sexual abuse compared to HC.

Within the BPD sample, there were 44 attempters (8 male, 36 female), 24 non-attempters (8 male, 16 female), with no significant difference by gender (i.e. attempters vs. non-attempters: ChiSq (1 df) = 1.98, p.n.s). Attempters were older than non-attempters (mean, (s.d.) = 29.6 (8.0) years vs. 25.9 (5.7) years, (t = 2.17, 61.1 df, p. = 0.034), with no significant differences between groups in SES, race, HamD-24 or GAS scores at the time of the scan. Importantly, there were no significant differences between attempters and non-attempters in proportions of subjects with any current co-morbid Axis I disorder at the time of the scan, or for lifetime diagnoses of MDD, AUD or PTSD, or for current use of psychoactive medications (i.e. attempters: 38.6%, non-attempters: 16.7%, ChiSq (1df) = 2.56, p. n.s.). A history of childhood sexual abuse (but not physical abuse) was more prevalent among suicide attempters compared to non-attempters (ChiSq 6.68, 1 df, p. = 0.01). There was no difference between groups in severity of overall borderline psychopathology, assessed by the DIB section scores.

Among BPD attempters, 19 were Low Lethality (1 male, 18 female) and 25 High Lethality attempters (7 male, 18 female), with no significant difference by gender (p = 0.11, Fisher's exact, 2 tailed). High Lethality attempters were significantly older than Low Lethality attempters (t = 2.03, 41.9df, p= 0.05), and had lower GAS scores at the time of the scan (t = 2.12, 39 df, p= 0.04). The two groups did not differ in SES, race, severity of depressed mood (HamD-24), or in proportions of subjects with any current co-morbid Axis I disorder at the time of the scan, or any lifetime MDD, AUD or PTSD. Use of psychoactive medication did not differ significantly between groups (i.e. High Lethality: 36%, Low Lethality 42.1%, ChiSq (1 df) = 0099, p. n.s.). Lethality status was not related to childhood history of sexual or physical abuse. The two groups did not differ in severity of overall BPD psychopathology.

2.1 Imaging Method—MRI scans were acquired with a 1.5T GE Signa Imaging System running version Signa 5.4.3 software (General Electric Medical Systems, Milwaukee, WI). A T1-weighted sagittal scout image was obtained for graphic prescription of the coronal and axial images. 3D gradient echo imaging (Spoiled Gradient Recalled Acquisition, SPGR) was

performed in the coronal plane (TR=25 ms, TE=5 ms, nutation angle=40°, FOV=24 cm, slice thickness=1.5 mm, NEX=1, matrix size=256×192) to obtain 124 images covering the entire brain. Additionally, a double echo-spin echo sequence was used to obtain T2 and proton density images in the axial plane to screen for neuroradiological abnormalities.

Structural MRI images were processed using SPM's diffeomorphic image registration algorithm (DARTEL) in SPM5 (Ashburner & Friston, 2001; Diwadkar, et al., in press) co-varied for age and gender. DARTEL optimizes the fidelity of shape-based deformations applied to fit native images in stereotactic space, outperforming all or most competing non-linear deformation algorithms (Klein et al., 2009). It is therefore optimized for assessing structural changes within a stereotactic framework, and well suited for VBM analyses. Following re-sampling (2 mm^3) and segmentation of T1-weighted images, a rigid gray matter template was created representing the average shape and size of the brains of all the subjects included in the study. Subjects' grey matter maps were warped to the coordinate system of the template, with Jacobian modulation used to scale native gray matter volume from native to MNI space (Good et al., 2001). This procedure has been extensively used in voxel-based analyses of gray matter images within the framework of random field methods.

VBM contrasts were conducted using 9 ROIs which have demonstrated differences between BPD and healthy control subjects in previous structural studies and included: the middle-inferior orbitofrontal cortex, anterior cingulate cortex, middle-superior temporal cortex, insula, hippocampus, parahippocampus, fusiform gyrus, lingual gyrus and amygdala. A hierarchical approach to group-wise analyses was employed to systematically assess gray matter differences between: a) Healthy control subjects compared to the total BPD sample, b) healthy control subjects against BPD sub-groups defined by attempter status, and, c) within BPD attempters, investigating the effects of lethality (High vs. Low Lethality attempters). Cluster level correction ($p<.001$) was employed to optimize sensitivity to detect clusters with minimal extent ($p_{thr}<.05$) (Ward, 2000).

All statistical analyses were conducted using a cluster-level correction approach that has been formally characterized (Ward, 2000) and utilized in several imaging related studies (Ladouceur et al., In Press; Hagler et al., 2006; Bakshi et al., 2011; Diwadkar et al., 2011a; 2011b; Diwadkar et al., In Press). The approach is based on "n" Monte Carlo simulations of the process of image generation, spatial correlations of voxels (i.e., clusters), voxel intensity thresholding (voxel-level values), probability thresholding, and minimum cluster size thresholding where the probability of a true positive detection of a significant cluster is determined from the simulations themselves.

The basic assumptions behind cluster level approaches is that true differences in imaging data will tend to occur over contiguous tissue or voxels, rather than individual voxels. We employed "n"=10^5 or 10,000 Monte Carlo simulations for data derived from each region of interest. For these simulations, we were interested in the frequency of occurrence of a minimum cluster size of contiguous voxels (voxel intensity $p<.05$) for 1 in 1000 instances, that is a cluster level correction of $p<.001$ (Ward, 2000; p 13). Thus the cluster extents in Table 2 reflect the minimum cluster size for the relevant region of interest that (based on 10,000 Monte Carlo simulations) for $\alpha<.001$ cluster level correction. Structural data from some subjects in this study were previously reported in contrasts between BPD and healthy control subjects (Soloff et al., 2008).

Results

1. Structural analyses

Results of structural analyses are presented in Table 2. In the contrast between all BPD subjects and healthy controls, BPD subjects had diminished grey matter concentrations in 7 of 9 ROIs, with most robust reductions in the insula (cluster size = 2844), with peak clusters in the left hemisphere, and in the middle superior temporal cortex (cluster size = 1440), with peak clusters in the right hemisphere (Fig. 1). Significant decreases in grey matter concentrations were also noted in hippocampus, fusiform gyrus, parahippocampus, anterior cingulate and amygdala, (in order of decreasing cluster sizes).

Compared to healthy controls, BPD attempters had diminished grey matter concentrations in 8 of 9 ROIs (Fig. 2). As noted in the contrast with all BPD subjects (above), the most robust decrease in grey matter concentration among BPD attempters was found in the insular cortex (cluster size = 2966), with peak clusters located in the left hemisphere. Insular cortex relays information from the limbic system, both physical and emotional, to the prefrontal regulatory systems. Diminished grey matter concentrations were also significant in middle-inferior orbital frontal cortex, important in mediating behavioral inhibition, and middle superior temporal cortex, which processes facial recognition, including assessment of threat. In concert with the insula, these structures are critical for adaptive responding to social stimuli. Amygdala was the only ROI which showed no significant difference between groups.

Compared to healthy controls, BPD non-attempters had diminished grey matter concentrations in 6 of 9 ROIs, with some noteworthy differences from the contrast with suicide attempters. Differences between groups were most robust in lingual gyrus (cluster size = 946), though decreased grey matter concentrations were also prominent in middle-superior temporal cortex (cluster size = 759), and insula (cluster size = 601). Lingual gyrus is part of a complex face recognition system, especially the assessment of angry faces and threat. Hippocampus, parahippocampus and amygdala showed no significant differences between groups.

Within the BPD sample, attempters had decreased grey matter concentrations in insular cortex compared to non-attempters, with peak clusters in the left hemisphere. In the reverse contrast, non-attempters had diminished grey matter concentrations in middle-superior temporal cortex, and lingual gyrus with peaks in the left hemisphere.

Among suicide attempters, those with High Lethality attempts had significant decreases in 6 of 9 ROIs compared to Low Lethality attempters. The most robust findings (in order of individual cluster size) indicate diminished grey matter concentrations in High Lethality attempters in middle-superior temporal gyrus (cluster size = 7752), middle-inferior orbital frontal gyrus (cluster size = 3403), and insular cortex (cluster size = 2168) (all with peak clusters in the right hemisphere), fusiform gyrus (cluster size = 1231), lingual gyrus (cluster size = 943) (with peaks in left hemisphere) and the parahippocampal gyrus (cluster size = 274) (with a peak cluster in the right hemisphere) (Fig. 3). Fusiform, lingual and parahippocampal gyrii process face recognition, facial emotion, and familiar scene recognition in social settings, relaying information forward to orbital frontal and superior temporal cortex.

Discussion

This is the first imaging study to specifically address structural brain changes associated with suicidal behavior in BPD. The relatively large sample size adds confidence to our

findings. We found significant differences in grey matter concentrations between BPD attempters and non-attempters, high and low lethality attempters, suggesting a possible role for specific neural circuits in suicidal behavior. Affected areas include orbital frontal, temporal, insular and paralimbic structures, broadly involved in emotion regulation, behavioral control, executive cognitive function and adaptive responding in social situations. Vulnerability to suicidal behavior in BPD, especially high lethality behavior, may be due to affective interference at times of stress with the specific behavioral functions of these structures.

Orbital frontal cortex: response inhibition and impulsivity

Diminished grey matter concentrations were found in high lethality compared to low lethality BPD attempters in middle-inferior orbital frontal cortex. Regulation of behavioral impulsivity and response inhibition are among the best studied functions of the orbital frontal cortex, and most relevant to suicidal behavior. Tasks involving inhibition of a prepotent response (e.g. the Go No-Go test) activate the orbital frontal cortex (Casey et al., 1997). Task performance on the Go No-Go test is impaired by lesions in the orbital frontal cortex in both animal and human studies (Fuster, 1989).

Impaired performance on the Go No-Go test, (i.e. responding when one should not), discriminates BPD from control subjects, and suicidal BPD subjects from BPD subjects with no suicidal behavior (Leyton et al., 1999).

An orbital frontal circuit connects the frontal monitoring systems with the limbic system and receives information concerning the internal state of the individual (Tekin & Cumming, 2002; Bonelli & Cummings, 2007). In concert with the anterior cingulate cortex (which mediates conflicts between competing choices), the orbital frontal cortex facilitates selection of external stimuli for attention and regulates response. The orbital frontal cortex is also a component part of a circuit that assesses emotion in facial expressions. Along with the fusiform gyrus and amygdala, the orbital frontal cortex is activated by angry faces (Blair et al., 1999). Positive covariation in activity occurs between Lt. amygdala and Rt. prefrontal cortex when perceiving negative faces, suggesting a neural mechanism for suppressing inappropriate responses to aversive stimuli in a social context (Iidaka et al., 2001). In BPD subjects, the connectivity between (Rt) orbital frontal cortex and ventral amygdala is decreased compared to healthy control subjects (New et al., 2008). Dysfunction in orbital frontal circuits results in behavioral disinhibition, aggression and emotional instability, all risk factors for suicidal behavior (Tekin & Cumming, 2002).

Middle-superior temporal cortex: perception of facial emotion

Diminished gray matter concentrations were found in high compared to low lethality BPD attempters in the middle-superior temporal cortex. In healthy control subjects, the superior temporal cortex (gyrus and sulcus) is involved in the perception of emotion, and where that emotion is being directed (Campbell et al, 1990). Superior temporal gyrus and sulcus are component parts of a complex face processing system (which also includes fusiform and lingual gyrii, amygdala and orbital frontal cortex). The superior temporal gyrus is activated by fearful faces (Radua et al., 2010; Iidaka et al., 2001). The superior temporal sulcus, in concert with the insula, fusiform gyrus and amygdala, analyzes bodily movements to provide information about the intentions of others (Frith & Frith, 1999; Allison & McCarthy, 2000). fMRI studies suggest that these structures mediate a rapid (“reflexive”) response to visual social inputs, especially negative visual stimuli (Koenigsberg, et al., 2009). Superior temporal sulcus is also involved in fear-based hypervigilance in attachment relationships (Buchheim et al., 2008).

In BPD subjects, viewing negative faces (angry, disgruntled faces) activates the superior temporal gyrus bilaterally, the Rt. middle temporal gyrus, Lt. amygdala and orbital frontal cortex (Iidaka et al., 2001). BPD subjects, compared to healthy controls, have decreased activation in Lt. middle-superior temporal gyrus and Rt. insula in response to negative IAPS pictures (compared to positive, or rest conditions) (Koenigsberg, et al., 2009). Adaptive responding to perceived negative social input may be compromised if these structures are impaired.

Insular cortex: co-operation, rejection sensitivity, and self awareness

Diminished grey matter concentrations were found in the insular cortex in BPD attempters compared non-attempters, and in high lethality compared to low lethality attempters. In a previous VBM study, we reported that insular cortex in BPD subjects was diminished in volume compared to healthy controls (Soloff et al., 2008). Diminished insular volumes have been associated with violent behavior in teenagers with BPD (Takahashi et al., 2009).

The insular cortex is considered a limbic integration area, a relay station for signals coming from the internal milieu to regulate homeostasis (Augustine, 1996). The insular cortex has widespread connections to the prefrontal and orbital cortex, temporal pole, superior temporal sulcus, anterior cingulate gyrus, amygdala, hippocampus, thalamus and associated limbic structures (Augustine, 1996). In social emotional interaction, it is involved in subjective awareness of one's emotional state, in bodily representation of emotion and in "mirroring" perceived emotion in others (i.e. "empathy")(New et al., 2008). In fMRI studies, the insula is activated by tasks which involve social interaction, trust and co-operation, but also social exclusion. BPD subjects show impaired anterior insula activation relative to healthy controls in a game of co-operation and reciprocity (an "economic exchange game") (King-Casas et al., 2008). A game mimicking social exclusion (the "cyber-ball game") leads to activation in anterior insula in BPD compared to control subjects (Eisenberger et al., 2003). Aversive personal autobiographical memories, (evolked by TAT images) (Schnell et al., 2007), and recall of personal unresolved life events (Beblo et al., 2006), activate insula in BPD subjects compared to controls. Negative emotion resulting from perceived rejection and social disappointment is among the most common precipitants to suicidal behavior in BPD. Impaired insula function may contribute to this vulnerability.

Fusiform, lingual and parahippocampal gyrii: processing faces and scenes

Diminished gray matter in fusiform, lingual and parahippocampal gyrii is found in high lethality compared to low lethality attempters. The fusiform and lingual gyrii are involved in facial recognition and in the perception of emotions in facial stimuli (Radua et al., 2010). The adjacent parahippocampal gyrus projects to the hippocampus and the limbic circuit, and plays a role in memory encoding and retrieval, especially in regard to retrieving information about the familiarity of scenes, complementing the functions of the fusiform face area. It also plays a role in identifying sarcasm in verbal communication (Rankin et al., 2009). Thus, it may help identify the social and emotional context of the scene. Retrieval of specific and positive autobiographical memories, a function of the hippocampus, is impaired in suicide attempters and related to poor problem solving (Williams & Broadbent, 1986). During an emotional crisis, this associative memory function enables a person to envision positive outcomes based on past experience.

Suicidal behavior in BPD is often precipitated by perceived rejection, abandonment, or social disapproval. We propose that abnormalities in the orbital frontal, temporal, insular and paralimbic structures found in attempters and high lethality attempters in this study would compromise adaptive responding to these negative emotional stressors. fMRI studies suggest that emotional stress (especially negative emotion) disrupts processing in neural

circuits responsible for emotion regulation, impulse control, executive cognitive function and episodic memory (Silbersweig et al., 2007; Minzenberg et al., 2007). Loss of cognitive inhibitory control in adverse social situations would increase the likelihood of impulsive, aggressive, self-destructive behavior in BPD.

Could structural differences between attempters and non-attempters, high and low lethality attempters be due to differences in BPD syndrome severity? These groups do not significantly differ on the DIB total section score suggesting that VBM differences associated with suicidality are independent of overall syndrome severity. Our research follows the stress-diathesis model of suicide advanced by Mann et. al. (1999 al. (2003). This model postulates a neurobiologic vulnerability to suicidal behavior, increasing the likelihood of suicidal behavior at times of stress. This biological vulnerability is expressed, in part, through behavioral traits of affective instability, impulsivity, aggression, and impaired executive cognitive functions. We propose that the structural anomalies identified in our contrasts of attempters and non-attempters, high and low lethality attempters, represent structural abnormalities in neural networks that mediate and regulate these functions. Whereas overall syndrome severity does not discriminate between groups, future analyses should look at the effects of specific personality traits (e.g. impulsivity, aggression) on structural changes in attempters and non-attempters, high and low lethality attempters.

Limitations

We were unable to control for medical consequences of suicide attempts, which may result in structural brain injury. This may be particularly relevant to differences between high and low lethality attempters. It is noteworthy that we found no differences between high and low lethality attempters in the hippocampus, which is sensitive to anoxic injury (Caine & Watson, 2000).

Structural brain differences between attempters and non-attempters, high and low lethality attempters may reflect the neurobiology of endophenotypic traits which contribute a diathesis to suicidal behavior, but are not specific for BPD, i.e. impulsive-aggression and emotion dysregulation. These traits are risk factors for suicide and may be found in other high risk disorders.

Structural brain abnormalities do not prove functional impairment. e.g. Functional impairment, demonstrated by fMRI, may be independent of structural abnormalities as demonstrated by VBM related morphometry (Diwadkar et al.2011). In this study, we found no volume loss in amygdala among BPD attempters compared to non-attempters or high versus low lethality BPD attempters, though fMRI studies have demonstrated abnormal hyperarousal of amygdala in BPD subjects in response to aversive pictures (Herpertz et al. 2001) or faces (Donegan et al. 2003). Hyperarousal of amygdala in response to negative emotional stimuli is believed to contribute to emotion dysregulation in BPD, a major risk factor for suicidal behavior (Silbersweig et al. 2007). We did find decreased volume of amygdala in the contrast of all BPD subjects compared to healthy controls, providing convergence with some previous studies (Driessen et al 2001, Tebarz van Elst et al. 2003, Schmahl et al. 2003, Soloff et al., 2008), but not all, (New et al. 2007, Zetzsche et al 2006, Irle et al 2005, Brambilla 2004).

fMRI, PET, and neuropsychological studies in BPD subjects have each demonstrated functional impairment related to the fronto-limbic structures identified in our study as potential mediators of suicidal behavior. However, there are no published fMRI studies targeting fronto-limbic functions (e.g. response inhibition, conflict resolution, episodic memory) in BPD subjects ascertained for suicidal behavior. These studies are currently underway in our laboratory.

Finally, while biologic diathesis plays a critical role in increasing the likelihood of suicidal behavior in BPD, psychosocial factors such as poor social and vocational function, prospectively predict suicidal behavior in our long term follow-up studies.

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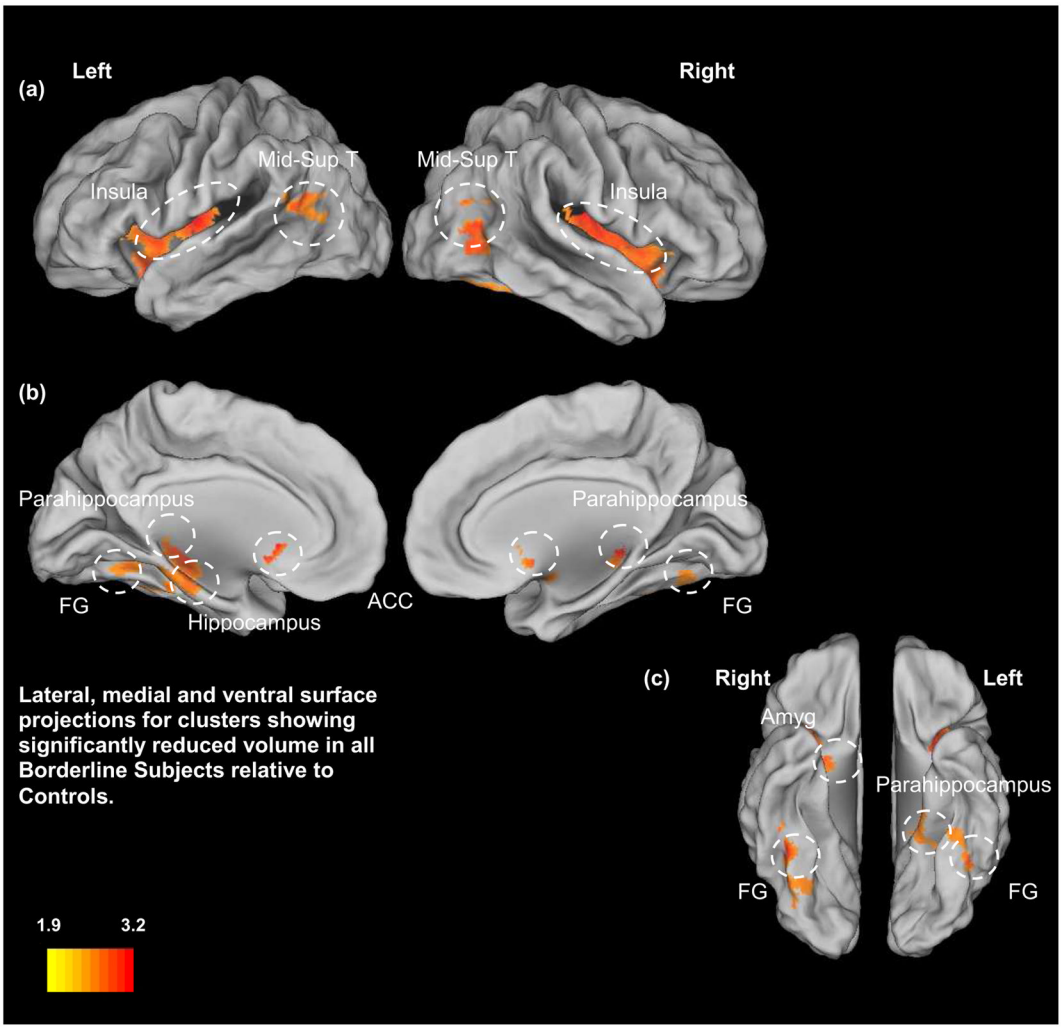

Figure 1.

The figure depicts reductions in gray matter volume in all BPD relative to controls assessed using DARTEL. Significant clusters (cluster level correction: $p<.001$) are projected to the cortical surface on bilateral lateral views (a), medial views (b) and ventral views (c). Collectively these ortho-projections convey volumetric reductions in brain regions relevant to BPD that are consistent with previous studies in independent samples. The regions with reductions including the insula, the middle and superior temporal cortex (Mid-Sup T), the fusiform gyrus (FG), the anterior cingulate cortex (ACC), the hippocampus and the parahippocampus and the amygdala (AMY).

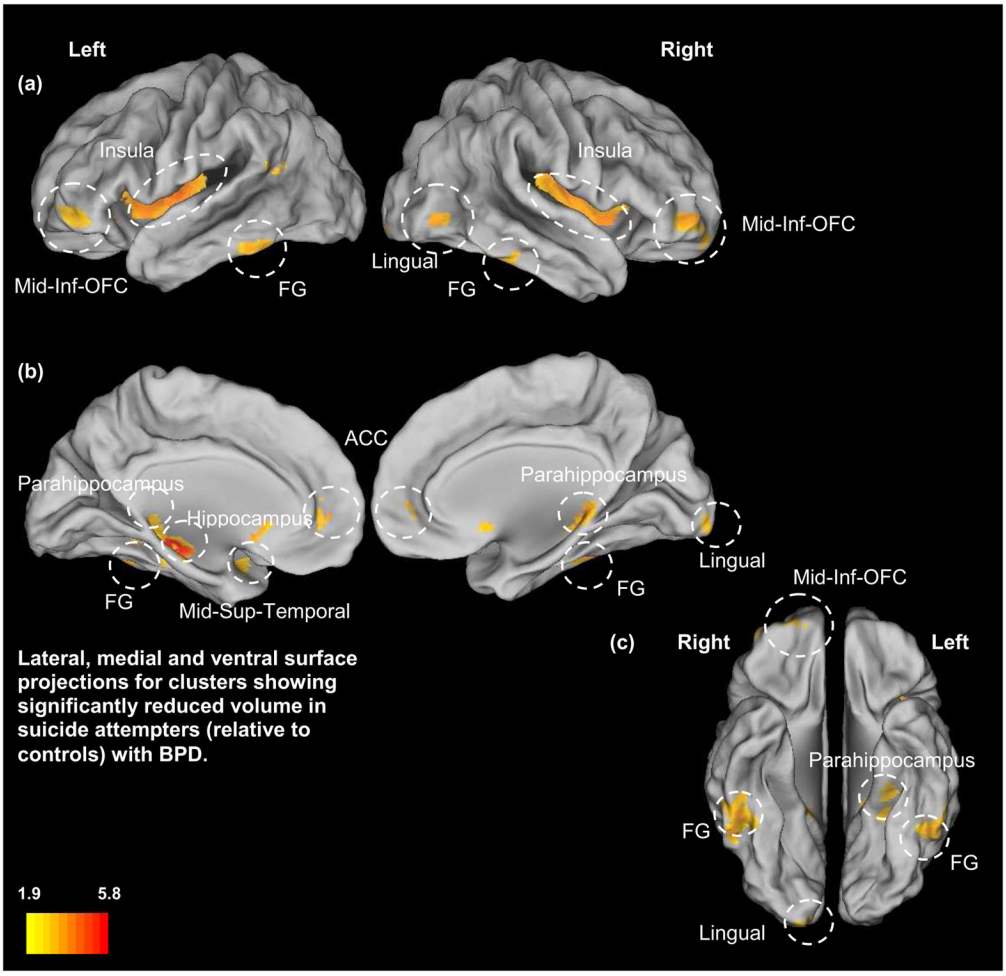

Fig. 2.

The figure depicts reductions in gray matter volume in BPD suicide attempters relative to controls assessed using DARTEL. Significant clusters (cluster level correction: $p<.001$) are projected to the cortical surface on bilateral lateral views (a), medial views (b) and ventral views (c) These ortho-projections convey robust volumetric reductions in BPD attempters in the insula, the middle and inferior orbito-frontal cortex (OFC), the fusiform gyrus (FG), the lingual gyrus, the anterior cingulate cortex (ACC), the mid.-sup. temporal cortex, the hippocampus and the parahippocampus.

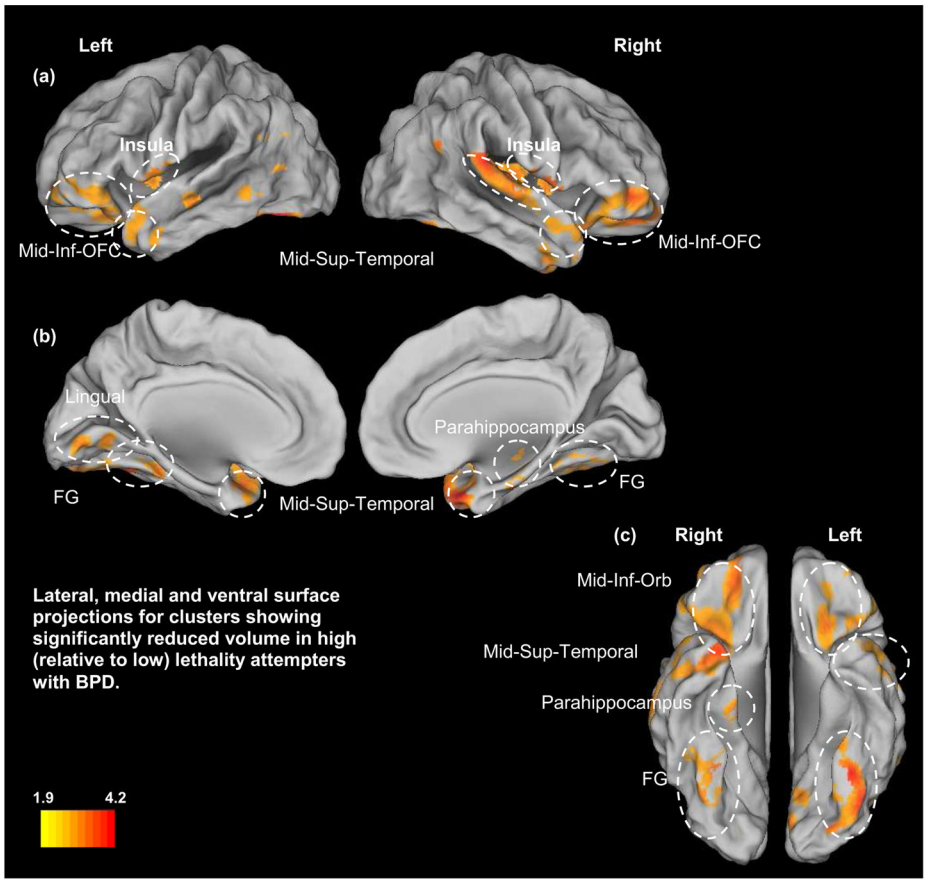

Fig. 3.

The figure depicts reductions in gray matter volume in high lethality suicide attempters relative to low lethality attempters assessed using DARTEL. Significant clusters (cluster level correction: $p<.001$) are projected to the cortical surface on bilateral lateral views (a), medial views (b) and ventral views (c). The naming schemes are consistent with Figure 1. High-lethality attempters show robust volumetric reductions in mid-sup. temporal cortex, mid-inf-OFC, insula, fusiform gyrus, lingual gyrus, and parahippocampus.

Table 1

Demographic, diagnostic and clinical characteristics of samples

	BPD (68)	Control (52)	t-test/ChiSq./p value
Female	52	24	X^2=11.70, df = 1, p.=.001
Male	16	28	
Age (s.d.)	28.3 (7.5)	25.9 (7.2)	t = 1.80, df =118, p.ns
SES (s.d.)	26.8 (12.0)	37.3 (14.8)	t = 4.06, df =88, p<.001
Race (%Cau.)	79.4%	71.2%	X^2 = 5.32, df = 5, p. ns.
HamD-24 (s.d.)	17.0 (8.1)	0.64 (1.1)	t =14.18, df=113, p.<.001
GAS (s.d.)	59.2 (9.5)	89.9 (5.2)	t = 19.90, df = 108, p.<.001
Physical abuse (%)	50	1	X^2 = 32.97, df=1, p.=.001
Sexual Abuse (%)	32.4	0	X^2 = 20.60, df =1, p,.001
MDD, current* (%)	63.2	n.a.	
MDD, lifetime* (%)	26.5	n.a	
PTSD, current (%)	14.7	n.a	
PTSD, lifetime (%)	25.0	n.a	
AUD, current (%)	23.5	n.a	
AUD, lifetime (%)	38.2	n.a	

*SCID current = diagnoses at time of scan. SCID lifetime excludes current diagnoses.

Table 2

Regions of Interest

	Cluster Extent Ind.		Voxel peak p (uncorr.)	Voxel Peak (x,y,z,)			Anatomical Location (TAL)
ROI	**p.001**	**Cluster**					
HC>BPD							
ACC	211	548	<.001	−8	22	−6	Lt. Ant Cingulate
Amygdala	118	192	.010	32	−6	−13	Rt. Amygdala
Fusiform	351	602	.003	43	−40	−15	Rt. Fusiform gyrus
Hip.	165	648	.001	33	−33	−3	Rt. Hip.
Insula	345	2844	.001	−39	−9	7	Lt. Insula
Lingual	222	<222	ns	--	--	--	--
Mid-inf OFC	416	<416	ns	--	--	--	--
Mid-Sup TP	752	1440	.003	56	−69	13	Rt. Mid temp gyrus
ParaHip	158	594	.005	−20	−28	−9	Lt. Parahipp. gyrus
HC>BPD-AT.							
ACC	107	498	.001	−3	9	−5	Lt.Ant.Cing.g.
Amygdala	89	<89	ns	--	--	--	--
Fusiform	134	302	.005	−47	−50	−15	Lt Fusiform g.
Hip.	67	187	.002	−27	−27	−10	Lt.Parahip. g.
Insula	290	2966	<.001	−41	−6	6	Lt Insula
Lingual	153	258	.001	19	−91	0.4	Rt. Lingual g.
Mid-inf OFC	190	782	<.001	36	51	−4	Rt. Mid. Fr. g.
Mid-Sup Tp	179	543	.001	−32	8	−16	Lt. Inf. Fr.g
ParaHip.	174	411	.001	18	39	5	Rt. Parahip.g
HC>BPD-NA							
ACC	143	237	.005	3	5	−3	Rt.Ant.Cing.g.
Amygdala	94	<94	ns	--	--	--	--
Fusiform	126	532	<.001	−25	−85	−13	Lt Fusiform g.
Hip.	66	0	ns	---	---	---	----
Insula	265	601	.01	40	−14	15	Rt Insula
Lingual	211	946	.002	−18	−85	−13	Lt. Lingual g.
Mid-inf OFC	196	301	.003	31	22	−23	Rt. Inf. Fr. g.

	Cluster Extent Ind.		Voxel peak p (uncorr.)	Voxel Peak (x,y,z,)			Anatomical Location (TAL)
ROI	**p.001**	**Cluster**					
Mid-Sup Tp	518	759	.003	30	19	−26	Rt.Temp.L.
ParaHip.	164	<164	ns	--	--	--	----
BPD-NA>BPD-ATT							
Insula	205	373	.008	−30	17	13	Lt. Insula
BPD-ATT>BPD-NA							
Lingual	205	1246	.001	−20	−83	−10	Lt. Lingual g
Mid-Sup Tp	544	1924	.001	−53	−47	2	Lt.Mid.Tp.g.
LOW LETH > HIGH LETH							
ACC	183	<183	ns	--	--	--	----
Amygdala	49	<49	ns	--	--	--	----
Fusiform	123	1231	<.001	−47	−69	−12	Lt.Fusiform g.
Hip.	94	<94	ns	--	--	--	----
Insula	238	2168	<.001	46	0	1	Rt.Insula
Lingual	275	943	.005	−12	−67	3	Lt.Lingual g.
Mid-inf OFC	315	3403	<.001	37	45	−7	Rt.Mid.Fr.g.
Mid-Sup TP	426	7752	<.001	28	15	−30	Rt.Sup.Tp.g.
ParaHip.	180	274	.009	22	−16	−26	Rt. Uncus