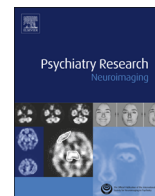




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# Impulsivity, aggression and brain structure in high and low lethality suicide attempters with borderline personality disorder



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## ABSTRACT

Impulsivity and aggressiveness are trait dispositions associated with the vulnerability to suicidal behavior across diagnoses. They are associated with structural and functional abnormalities in brain networks involved in regulation of mood, impulse and behavior. They are also core characteristics of borderline personality disorder (BPD), a disorder defined, in part, by recurrent suicidal behavior. We assessed the relationships between personality traits, brain structure and lethality of suicide attempts in 51 BPD attempters using multiple regression analyses on structural MRI data. BPD was diagnosed by the Diagnostic Interview for Borderline Patients–revised, impulsivity by the Barratt Impulsiveness Scale (BIS), aggression by the Brown–Goodwin Lifetime History of Aggression (LHA), and high lethality by a score of 4 or more on the Lethality Rating Scale (LRS). Sixteen High Lethality attempters were compared to 35 Low Lethality attempters, with no significant differences noted in gender, co-morbidity, childhood abuse, BIS or LHA scores. Degree of medical lethality (LRS) was negatively related to gray matter volumes across multiple fronto-temporal–limbic regions. Effects of impulsivity and aggression on gray matter volumes discriminated High from Low Lethality attempters and differed markedly within lethality groups. Lethality of suicide attempts in BPD may be related to the mediation of these personality traits by specific neural networks.

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## 1. Introduction

Personality traits such as impulsivity and aggressiveness are associated with suicidal behavior across diagnoses. In a stress–diathesis model of suicide, they represent vulnerable temperaments, and predispositions to impulsive and aggressive behavior in response to specific trigger events (for review, see Mann et al., 1999; Mann, 2003). Trait dispositions such as impulsivity and aggressiveness may be heritable (e.g., as endophenotypes), or acquired in the course of development (e.g., through childhood abuse). In neuroimaging studies, they have been associated with variations in the structure and function of brain networks that regulate mood, impulse and behavior. At times of emotional stress, dysfunction in these neural networks may result in interference with executive cognitive functions, such as response inhibition, conflict resolution, and recall of episodic memory (for review, see Fertuck et al., 2006). As a result, problem solving and adaptive coping are impaired, increasing the likelihood of impulsive or aggressive behavior. We study the relationship between personality

characteristics, brain function and suicidal behavior in the context of borderline personality disorder (BPD), a personality disorder defined, in part, by recurrent suicidal behavior, impulsivity and aggression. With a suicide rate of 3–10% and a community prevalence estimated at 1% of the population, BPD is a clinically relevant model for the study of suicide (Swartz et al., 1990).

There is a paucity of neuroimaging studies in BPD subjects ascertained specifically for suicidal behavior. In a voxel-based morphometry study (VBM) comparing BPD suicide attempters with BPD non-attempters, we recently reported specific structural differences in BPD subjects associated with suicidal behavior, and differences between High Lethality and Low Lethality suicide attempters (Soloff et al., 2012). BPD attempters had diminished gray matter concentrations in left insular cortex compared with BPD non-attempters. High Lethality attempters had diminished gray matter compared with Low Lethality attempters in an extensive fronto–limbic network including the following regions: right middle–inferior orbital frontal cortex, right middle–superior temporal cortex, right insular cortex, left fusiform gyrus, left lingual gyrus, and right parahippocampal gyrus. These areas are broadly involved in emotion regulation, behavioral control, and adaptive responding to social situations. Suicide researchers have long maintained that suicide attempters and completers represent

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separate but overlapping populations, with differing clinical characteristics (Maris et al., 2000). High Lethality attempters share many clinical characteristics with patients who complete suicide and may share neurobiological vulnerabilities related to high-risk personality traits such as impulsivity and aggressiveness.

To assess the relationships between personality traits, brain structure, and suicidal behavior, we used a multiple regression analysis of VBM data in High and Low Lethality BPD attempters to map the relationships between impulsivity, aggression and gray matter in key brain structures.

## 2. Methods

### 2.1. Subjects

Subjects for this study were recruited by advertisement from the outpatient programs of the Western Psychiatric Institute and Clinic and surrounding community to participate in a longitudinal study of suicidal behavior in BPD. The study was approved by the Institutional Review Board of the University of Pittsburgh, and funded by the National Institute of Mental Health. 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 or DSM IV (SCID) (Spitzer et al., 1988; First et al., 2005). (Because this is a longitudinal study, DSM-IV was added when it first became available.) Axis II diagnoses were established 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 scored 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, schizoaffective 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 Axes 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 the time of their annual follow-up assessment. As a result, all subjects had updated SCID interviews for current diagnoses. Aggression was assessed by interview on the Brown–Goodwin Lifetime History of Aggression (LHA) (Brown et al., 1979) and trait impulsivity by self-report questionnaire using the Barratt Impulsiveness Scale (BIS) (Barratt, 1965). The 24 item Hamilton Rating Scale for Depression (HamD) was obtained before the scan as a measure of depressed mood (Guy, 1976). High Lethality status among attempters was defined as a lifetime maximum Lethality Rating Scale score (LRS) of 4 or more. (For example, for a suicide attempt by overdose with sedative drugs, an LRS 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 1 week before the scan. Female subjects were required to have a negative screen for pregnancy. All subjects had a negative urine toxicology screen for abuse immediately before the scan. Some BPD subjects were taking psychoactive medication.

### 2.2. Imaging method

Magnetic resonance imaging (MRI) was performed with a 1.5T GE Signa Imaging System running version Signa 5.4.3 software (General Electric Medical Systems, Milwaukee, WI, USA). A T<sub>1</sub>-weighted sagittal scout image was obtained for graphic prescription of the coronal and axial images. Three-dimensional gradient echo imaging (Spoiled Gradient Recalled Acquisition, SPGR) was performed in the coronal plane (repetition time=25 ms, echo time=5 ms, nutation angle=40°, field of view=24 cm, slice thickness=1.5 mm, number of excitations=1, and matrix size=256 × 192) to obtain 124 images covering the entire brain. Additionally, a double echo–spin echo sequence was used to obtain T<sub>2</sub> and proton density images in the axial plane to screen for neuroradiological abnormalities.

Structural MR images were preprocessed using the Statistical Parametric Mapping (SPM) diffeomorphic image registration algorithm (DARTEL) in SPM8 (Friston et al., 1995; Ashburner, 2007; Diwadkar et al., 2011). DARTEL optimizes the fidelity of shape-based deformations applied to fit native images in stereotaxic space, and performs favorably relative to other non-linear deformation algorithms (Klein et al., 2009). It is therefore optimized for assessing structural changes within a stereotaxic framework, and well suited for VBM analyses. Following resampling (2 mm<sup>3</sup>) and segmentation of T<sub>1</sub>-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' gray matter maps were then warped to the coordinate system of the template, with the Jacobian modulation used to scale native gray matter volume from native to Montreal Neurological Institute (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. Structural data for 44 BPD attempters were previously included in a larger study comparing BPD attempters, non-attempters and healthy control subjects (Soloff et al., 2012). Our findings from that structural analysis, defining deficits associated with lethality, were used to define regions of interest in this analysis. First, we defined a regional mask corresponding to clusters of significance ( $P < 0.05$ , cluster level) identifying reductions in gray matter volume in High (relative to Low) Lethality attempters (Ward, 2000). This regional mask spanned nine regions of interest including the following: the middle-inferior orbital frontal cortex, anterior cingulate cortex, middle-superior temporal cortex, insula, hippocampus, parahippocampus, fusiform gyrus, lingual gyrus and amygdala (Soloff et al., 2008; Leichsenring et al., 2011).

Personality trait variables (LHA and BIS) were entered individually in multiple regression analyses as co-variables of interest to investigate the positive and negative effects of these clinical measures on brain structures in High and Low Lethality suicidal subjects (Friston et al., 1995). These methods follow previous investigations of effects of symptom or personality dimensions on regional brain structure (Banissy et al., 2012). Cluster level correction ( $P_c < 0.05$ ) was used to optimize sensitivity to detect clusters with minimal extent (cluster forming threshold,  $P_{thr} < 0.05$ ) (Ward, 2000).

## 3. Results

### 3.1. Sample characteristics

There were 51 BPD attempters subdivided as follows: 16 High Lethality (5 male, 11 female) and 35 Low Lethality attempters (5 male, 30 female), with no significant group differences by gender, race or socioeconomic status (Table 1). The mean (S.D.) age of the sample was 30.1 (8.1) years with a range of 18–47 years. High Lethality attempters were significantly older (36.1 (9.2) years) than Low Lethality attempters (27.4 (5.9) years),  $t = 3.47$ , d.f. = 20.95,

**Table 1**  
Characteristics of the sample<sup>a</sup>.

	High Lethality	Low Lethality	Statistics (t, d.f., P or $\chi^2$ , d.f., P)**
N (M/F)	16 (5 M/11 F)	35 (5 M/30 F)	$\chi^2 = 2.00$ , d.f. = 1, $P = n.s.$
Age (years, S.D.)	36.1 (9.2)	27.4 (5.9)	$t = 3.47$ , d.f. = 20.95, $P = 0.002$
Race (%Cau.)	75	74.3	$\chi^2 = 0.003$ , d.f. = 1, $P = n.s.$
Educ. (% > 12 years)	56.3	62.9	$\chi^2 = 0.20$ , d.f. = 1, $P = n.s.$
SES			
Low = 2 + 3	10	23	
High = 4 + 5	6	12	$\chi^2 = 0.05$ , d.f. = 1, $P = n.s.$
Abused (%yes)	43.8	37.1	$\chi^2 = 0.20$ , d.f. = 1, $P = n.s.$
MDD (%yes)	75	60	$\chi^2 = 1.08$ , d.f. = 1, $P = n.s.$
Alcohol (%yes)	6.3	17.1	$\chi^2 = 1.10$ , d.f. = 1, $P = n.s.$
Other drugs (%yes)	31.3	14.3	$\chi^2 = 2.01$ , d.f. = 1, $P = n.s.$
Anxiety dx. (%yes)	50	65.7	$\chi^2 = 1.14$ , d.f. = 1, $P = n.s.$
PTSD (%yes)	18.8	8.6	$\chi^2 = 1.10$ , d.f. = 1, $P = n.s.$
Psych. meds (%yes)	50.0	37.1	$\chi^2 = 0.75$ , d.f. = 1, $P = n.s.$
HamD	18.1 (10.0)	16.3 (7.9)	$t = 0.68$ , d.f. = 49, $P = n.s.$
BIS	73.5 (5.2)	74.7 (4.8)	$t = 0.82$ , d.f. = 49, $P = n.s.$
LHA	15.6 (8.4)	16.5 (6.3)	$t = 0.39$ , d.f. = 49, $P = n.s.$

\*\* t, d.f., P: Student's t-test, 2 tailed.  $\chi^2$ , d.f., P: Chi Square test, 2 tailed.

<sup>a</sup> SCID Axis I co-morbidity at time of scan. Alcohol and Other drugs include abuse and/or dependence, anxiety dx includes any anxiety disorder except PTSD.

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