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ORIGINAL ARTICLE

Fronto-limbic brain structures in suicidal and non-suicidal female patients with major depressive disorder

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Our knowledge about the neurobiology of suicide is limited. It has been proposed that suicidal behavior generally requires biological abnormalities concomitant with the personality trait of impulsivity/aggression, besides an acute psychiatric illness or psychosocial stressor. We investigated fronto-limbic anatomical brain abnormalities in suicidal and non-suicidal adult female patients with unipolar depression. Our sample consisted of seven suicidal unipolar patients, 10 non-suicidal unipolar patients and 17 healthy female comparison subjects. The criterion for suicidality was one or more documented lifetime suicide attempts. A 1.5T GE Signa Imaging System running version Signa 5.4.3 software was used to acquire the magnetic resonance imaging images. All anatomical structures were measured blindly, with the subjects' identities and group assignments masked. We used analysis of covariance with age and intracranial volume as covariates and the Tukey–Kramer procedure to compare suicidal patients, non-suicidal patients and healthy comparison subjects. Suicidal patients had smaller right and left orbitofrontal cortex gray matter volumes compared with healthy comparison subjects. Suicidal patients had larger right amygdala volumes than non-suicidal patients. Abnormalities in the orbitofrontal cortex and amygdala in suicidal patients may impair decision-making and predispose these patients to act more impulsively and to attempt suicide.
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Introduction

The risk for suicide is 10–20 times higher in people with mood disorders than in the general population[1] and our knowledge about the neurobiology of suicide is still limited. Although suicide is a potentially preventable cause of death, efforts to reduce suicide rates have had minimal success. The clinical markers of patients at high risk for suicide may detect most patients who will commit suicide, but may also be found in a large number of patients who will never commit suicide.[2] Understanding the neural correlates of suicidal behavior may be helpful in reducing suicide rates in major depression and other psychiatric disorders.

Serotonergic and noradrenergic abnormalities in regions of the prefrontal cortex, as well as the dorsal raphe nucleus and locus ceruleous are implicated in suicide. Neurochemical studies show that there is serotonin hypofunction in suicide victims, there are fewer presynaptic serotonin transporter binding sites and more post-synaptic serotonin receptors in their

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prefrontal cortex.[3,4] Post-mortem studies[3] as well as *in vivo* studies[5] demonstrate that reduced serotonergic activity in cerebrospinal fluid is associated with increased suicide risk. It has been proposed that suicidal behavior generally requires an acute psychiatric illness or psychosocial stressor, a predisposing factor (such as the personality trait of impulsivity/aggression) and concomitant biological abnormalities.[6] Impulsivity and a disturbed regulation of anxiety or aggression may represent risk factors for suicidal behavior that cut across diagnostic boundaries.[7,8] Tebartz van Elst *et al*.[9–11] proposed that a dual brain pathology might be responsible for the hyperarousal and dyscontrol states seen in patients with impulsivity and affective-aggressive episodes. According to this proposal, abnormalities of the amygdala result in dysfunctional arousal states, and abnormalities of the prefrontal cortex result in dyscontrol states.[9–11]

Structural magnetic resonance imaging (MRI) studies demonstrate volumetric abnormalities in the prefrontal subregions and the limbic structures, that is, hippocampus and amygdala, in patients with major depressive disorder.[12,13] Post-mortem studies complement these results and indicate reduced density and number of glial cells in the subgenual anterior cingulate gyrus and orbitofrontal cortex,[14] and amygdala[15] in major depressive disorder. As Strakowski *et al*.[12] articulate, relatively diminished prefrontal modulation on an anterior limbic network may result in dysregulation of mood. Periventricular and subcortical white matter changes disrupting critical neuroanatomic pathways may contribute to mood dysregulation. Unipolar patients with a history of suicide attempt have significantly more subcortical gray matter hyperintensities compared to unipolar patients without a history of suicide attempt.[16] Furthermore, there is a higher prevalence of periventricular white matter hyperintensities in young adults with unipolar depression and a history of a suicide attempt[17] compared to depressed young adults without such a history. These findings suggest that gray and white matter hyperintensities might represent brain abnormalities that could be markers for higher risk for suicide attempts.

Further work is clearly indicated to explore the associations between neuroimaging findings and suicidal behavior. We investigated fronto-limbic anatomical brain abnormalities in suicidal and non-suicidal adult female patients with unipolar depression, with a hypothesis that suicidal patients would have more pronounced fronto-limbic abnormalities than non-suicidal ones.

Materials and methods

Our sample consisted of seven suicidal, 10 non-suicidal female unipolar patients and 17 healthy female controls. The University of Pittsburgh Institutional Review Board approved the study protocol, and all subjects gave written informed consent after receiving a detailed description of the study. All 17 depressed subjects met diagnostic inclusion criteria for Major Depressive Disorder as determined by the Structured Clinical Interview for DSM-IV (SCID).[18] All patients were medication-free for at least 2 weeks immediately preceding the study. All subjects were right-handed. The criterion for suicidality was one or more documented suicide attempts. Clinical ratings were carried out using the Hamilton Depression Rating Scale (HDRS).[19] At the time of study participation, five of the suicidal patients were depressed and two were euthymic. Seven of the non-suicidal patients were depressed and three were euthymic. Exclusion criteria were any other DSM-IV axis I comorbidity, current medical problems, history of neurological illness, history of head trauma with loss of consciousness, or history of substance or alcohol abuse/dependence at any time.

We recruited healthy controls by advertisement and assessed them with the Structured Clinical Interview for DSM-IV, non-patient edition (SCID-NP). Exclusion criteria included any DSM-IV axis I diagnosis, current medical problems, history of neurological illness, history of head trauma with loss of consciousness, and positive history of psychiatric disorders or suicide among first-degree relatives. Healthy controls were matched, as a group, with unipolar patients for age, gender and race.

Image acquisition

A 1.5T GE Signa Imaging System running version Signa 5.4.3 software (General Electric Medical Systems, Milwaukee, WI, USA) was used to acquire the MRI scans. A 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) in order to obtain 124 images covering the entire brain.

Image analysis

All images, except for orbitofrontal cortex measurements, were analyzed blindly using Scion Image for Windows Beta-3b version on a PC workstation (Scion Corporation Inc., Frederick, MD, USA). The orbitofrontal cortex measures were conducted with the BRAINS2 software, developed at the University of Iowa Hospitals and Clinics. For the BRAINS2 tracings, the images were spatially realigned, so that the brain anterior–posterior axis was parallel to the AC-PC line, which was horizontal in the sagittal plane, and the interhemispheric fissure was vertical in the axial plane. All raters, who met the inter-rater agreement standard of intraclass correlation coefficients for each of the regions of >0.90 versus a second independent rater, did all anatomical measurements with the subjects' identity and group assignment masked. Intracranial volumes were manually traced and measured in the coronal plane.

Regions-of-interest

The regions of primary interest were the orbitofrontal cortex, cingulate, amygdala and hippocampus, because previous neuroimaging studies of depressed patients have mainly shown anatomical and functional abnormalities in these brain regions.[12,13]

A detailed description of the geometrical method utilized to measure the orbitofrontal cortex is presented elsewhere.[20]

We started tracing the amygdala on the coronal slice where the mammillary bodies first appeared. The superior and lateral borders were distinguished by the temporal lobe white matter. The inferior border was the parahippocampal gyrus white matter. The anterior border was the place where the amygdala gray matter could no longer be distinguished from the rest of the temporal lobe.[21]

Hippocampus tracing started on the coronal slice where the thalamus was connected with the superior colliculus and finished one slice before the mammillary bodies appeared. The superior border was the corona radiata, and then, going anteriorly, the ambient cistern. The inferior border was the white matter, and the lateral border was the inferior horn of the lateral ventricle.[21]

The cingulate was divided into four sections, anterior and posterior, right and left. All tracing of the cingulate were performed in the coronal view. The first slice traced was two slices anterior to the final slice where the genu was visible. Tracing was continued until the anterior commissure was apparent, and it marked the posterior limit of the anterior cingulate. The subsequent slice marked the anterior border of the posterior cingulate. The final slice measured was the one where the cerebral aqueduct appeared within the pons.[22]

As exploratory analyses, we also measured the lateral ventricles, caudate, putamen, thalamus, temporal lobe, superior temporal gyrus, dorsolateral prefrontal cortex and subgenual prefrontal cortex. The tracing methods for these structures are presented elsewehere.[23–26]

Statistical analysis

All statistical analyses were conducted using the SYSTAT (SPSS Science, Chicago, IL, USA) software, version 8, and a 2-tailed statistical significance level was set at $P<0.05$. Length of illness, age at onset, number of previous episodes and Hamilton Depression (Ham-D) scores were compared using Mann–Whitney *U*-tests. Family history, episode type, education status and previous antipsychotic usage were compared using Fisher's Exact Test. We used analysis of covariance, adjusting for age and intracranial volume followed by the Tukey–Kramer procedure to compare adjusted mean structure volumes of suicidal patients, non-suicidal patients and healthy comparison women.

Results

Suicidal and non-suicidal patients did not differ in number of previous episodes, length of illness, age at illness onset and Ham-D scale scores (Table 1). The education status was not different between the two groups ($P=0.810$). There were no significant differences in family history for mood disorders and previous antipsychotic usage between suicidal and non-suicidal patients (Pearson χ^2, $P=1.000$ for both). There were no significant differences among the three groups with respect to age (mean $\pm$ s.d. = 31.4 ± 13.9 year for suicidal patients; 36.5 ± 7.5 year for non-suicidal patients; and 31.3 ± 8.3 year for healthy women) (univariate analysis of variance, df = 2,31, $F=1.042$, $P=0.37$).

Table 2 shows the results of the overall analysis of covariance testing for the brain regions of primary interest. Pairwise comparisons showed that suicidal patients had smaller right ($P=0.01$) and left ($P=0.02$) orbitofrontal cortex gray matter volumes compared with healthy women (Figure 1). Suicidal patients had larger right amygdala ($P=0.04$) volumes than non-suicidal patients (Figure 2). Non-suicidal patients did not differ from healthy women on any of the measures. The volumes of the regions of primary interest (orbitofrontal cortex, cingulate, amygdala and hippocampus) were not correlated with the number of previous episodes, length of illness and age at onset (Pearson correlations, uncorrected, all $P>0.05$).

Discussion

We compared female unipolar patients, with a history of a documented suicide attempt and without a history of suicide attempt and healthy women. The

Table 1 Clinical characteristics of suicidal and non-suicidal patients

	Suicidal patients (n = *7*)	*Non-suicidal patients* (n = *10*)	P
Length of illness (years)	15.6 ± 15.0	9.7 ± 11.6	0.30
Age at onset (years)	16.0 ± 4.5	26.9 ± 10.5	0.07
No. of previous episodes	18.6 ± 35.6	3.9 ± 3.4	0.18
Ham-D scores	13.7 ± 10.9	10.9 ± 8.0	0.62

Abbreviation: Ham-D scores, Hamilton Depression scores.
Mann–Whitney *U*-test, with exact significance (2-tailed).

Table 2 Volumes (cm^3) of brain regions of primary interest in suicidal and non-suicidal patients and healthy individuals

Region	*Suicidal patients* (n = *7*)	*Non-suicidal patients* (n = *10*)	*Healthy controls* (n = *17*)	*F*	*df*	P
OFC, right gray	6.06 ± 1.06	6.84 ± 1.31	8.09 ± 1.46	5.793	2,29	0.008
OFC, left gray	5.32 ± 0.59	6.10 ± 1.38	7.17 ± 1.51	4.470	2,29	0.02
Amygdala, right	2.46 ± 0.29	1.90 ± 0.45	2.08 ± 0.43	3.594	2,29	0.04
Amygdala, left	2.05 ± 0.37	1.91 ± 0.44	1.99 ± 0.39	0.343	2,29	0.71
Hippocampus, right	3.35 ± 0.49	3.47 ± 0.42	3.29 ± 0.34	0.291	2,29	0.75
Hippocampus, left	3.44 ± 0.70	3.38 ± 0.43	3.32 ± 0.27	0.121	2,29	0.89
Cingulate, right posterior	2.20 ± 0.30	2.83 ± 0.60	2.68 ± 0.60	2.916	2,29	0.07
Cingulate, right anterior	2.66 ± 0.26	3.10 ± 0.54	3.00 ± 0.56	1.538	2,29	0.23
Cingulate, left posterior	2.63 ± 0.51	2.73 ± 0.56	2.67 ± 0.43	0.205	2,29	0.82
Cingulate, left anterior	2.73 ± 0.48	2.74 ± 0.62	3.17 ± 0.52	2.126	2,29	0.14

Abbreviation: OFC, orbitofrontal cortex.
Unadjusted means and standard deviations are shown.

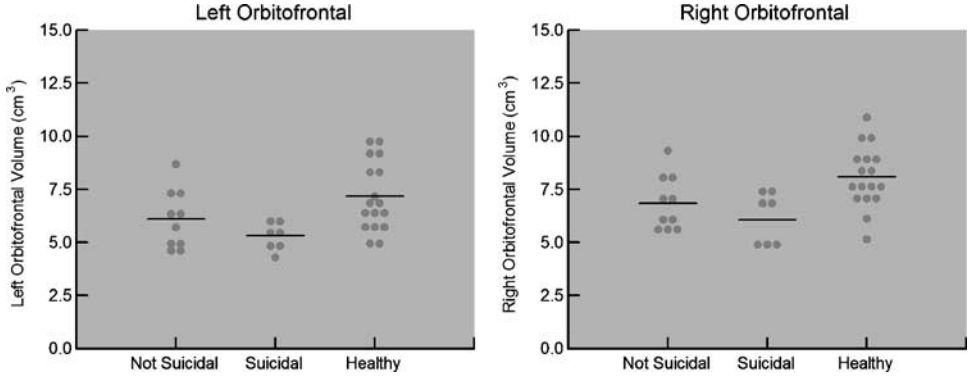

Figure 1 Right and left orbitofrontal cortex gray matter volumes in suicidal and non-suicidal patients and healthy women. *Note*: Suicidal patients ($n = 7$) had smaller right ($F = 5.793$, $df = 2,29$, $P = 0.008$) and left ($F = 4.470$, $df = 2,29$, $P = 0.02$) orbitofrontal cortex gray matter volumes compared with healthy women ($n = 17$).

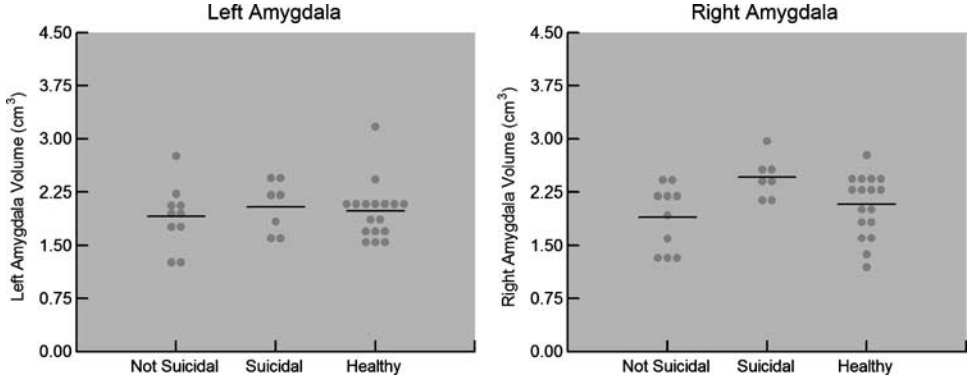

Figure 2 Right and left amygdala volumes in suicidal and non-suicidal patients and healthy women. *Note*: Significant difference between suicidal ($n = 7$) and non-suicidal ($n = 10$) patients for right amygdala volumes ($F = 3.594$, $df = 2,29$, $P = 0.04$).

main findings of this analysis are that unipolar patients with a history of a suicide attempt had smaller right and left orbitofrontal cortex gray matter volumes compared with healthy women, and larger right amygdala than non-suicidal patients. The involvement of both orbitofrontal cortex and amygdala is intriguing, as these are two critical regions involved in goal-directed behavior, judgment and decision-making abilities that are most often impaired in patients with unipolar depression.[27,28]

Few studies have examined the volume of orbitofrontal cortex in patients with unipolar depression. Two studies in mid-life depression[29,30] reported smaller orbitofrontal cortex volumes in patients compared to healthy comparison subjects. One possible explanation for this, as put forth by Bremner *et al.*,[29] is the glucocorticoid toxicity that occurs with repeated episodes, although this has not been selectively studied for orbitofrontal cortex. Patients with depression have a long-lasting hyperactivity of the corticotropin-releasing hormone (CRH) neurons, resulting in increased stress responsiveness and reflecting a glucocorticoid resistant state.[31] Patients with multiple episodes of depression exhibit greater cortisol levels after CRH than first-episode depressive patients and healthy controls,[32] and there is down-regulation of CRH receptors in the frontal cortex of victims of suicide.[33] In our analysis, although statistically not significant, suicidal patients had more previous episodes than non-suicidal patients, and they had an earlier age of illness onset; both of which could have led to greater glucotoxicity. It could also be that suicidal patients have smaller orbitofrontal cortices at birth (i.e. impaired neurodevelopment), which predispose them to impaired decision-making and impulsivity.

Orbitofrontal cortex plays a main role in decision-making and predicting expected outcomes. Lower levels of ventromedial activity are associated with higher suicidal behavior and higher lethality of the act.[34] Our finding of smaller orbitofrontal cortex volumes in suicidal patients complements the findings of a recent study, which showed that suicide attempters have a specific impairment in decision-making, regardless of their affective state.[35] These authors suggest that impairment in decision-making is associated with a susceptibility to suicidal behavior, rather than a susceptibility to affective disorders. Patients with orbitofrontal cortex and amygdala lesions exhibit patterns of behavior often described as impulsive, and they are often unable to adjust their behavior appropriately to the contingencies of the task, as seen in their performance on gambling tasks.[36] Recently, a component of impulsivity called 'lack of premeditation' (engaging in an act without thinking or reflecting on its consequences) was found to be linked to disadvantageous decision making.[37] The 'somatic marker hypothesis' proposes that decision making is a process that depends on emotion, and that both the orbitofrontal cortex and the amygdala play parts in it.[36] The orbitofrontal cortex plays an important role in the regulation of emotional responses and behavior guided by predicted outcome, through inhibition of amygdala.[38]

Our findings could also be seen in the context of the 'dual brain pathology' theory proposed by Tebartz van Elst *et al.*[9–11] The relatively diminished prefrontal modulation of the anterior limbic network (e.g. amygdala, thalamus, anterior striatum) and resulting dysregulation of mood[12] might also contribute to poor decision-making and impulsivity in suicide attempters. The amygdala and orbitofrontal cortex cooperate to encode the learning of goal-directed behavior,[27,38] as the amygdala encodes the emotional significance of external stimuli, and the orbitofrontal cortex uses this information to adapt the behavior according to the current needs of the individual. Right, but not left, amygdala connectivity with bilateral orbitofrontal cortices is decreased during unconscious processing of behaviorally relevant stimuli.[39] Increased amygdala volumes have been reported in depressed female[10] and bipolar[40,41] patients. One study reported significantly larger amygdala volumes in patients with first-episode versus recurrent major depression.[42] The authors explained this finding in the light of higher neural activity in the amygdala in the first-episode group and longer exposure to antidepressant medication in the recurrent major depression group.[42] It is hard to explain why suicidal patients had larger right amygdala volumes than non-suicidal patients in our analysis, and this finding needs to be replicated.

One possible explanation for the finding that the suicidal patients had more brain abnormalities than the non-suicidal patients may be that suicidal patients comprise a more severe phenotype of the disorder, with an earlier age of onset and more prior depressive episodes and longer disease duration. To explore more about the effect of these confounding variables on the brain regions of interest we examined, we performed correlation analyses to see whether these confounding variables correlated with the brain changes we reported, and none of the correlations were statistically significant.

We did not find any evidence of changes in the hippocampus of suicidal patients. Although the hippocampus is one of the major limbic structures implicated in the pathophysiology of mood disorders, there is no consensus concerning a link between hippocampal volume change and major depression. Some studies report decreased hippocampal volumes, whereas others report normal hippocampal volumes in unipolar patients versus healthy subjects.[43] Also, there are reports that antidepressants may block or even reverse hippocampal atrophy.[43] The lack of significant findings in our study for the hippocampus may be due to previous antidepressant exposure, which we did not control for.

There are several limitations of our analysis. The severity of the illness was measured by comparing the age at onset, number of episodes and the severity of the affective episode at the time of MRI scans; and there was no difference in illness severity for the episode of depression at the time the MRI scans were performed. However, the severity of the episode in which the suicide attempt took place might be a more important variable,[16] and we did not have access to that information. This also applies to their MRI scans before or at the time of the suicide attempt. Our analysis involved a relatively small sample size. These findings are limited to women and need to be replicated. Yet, the changes we observed in the

orbitofrontal cortex and amygdala in suicidal patients may be important in understanding the basis of the suicidal behavior.

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