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Left orbitofrontal and superior temporal gyrus structural changes associated to suicidal behavior in patients with schizophrenia

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ABSTRACT

Suicidal attempts are relatively frequent and clinically relevant in patients with schizophrenia. Recent studies have found gray matter differences in suicidal and non-suicidal depressive patients. However, no previous neuroimaging study has investigated possible structural abnormalities associated to suicidal behaviors in patients with schizophrenia. A whole-brain magnetic resonance voxel-based morphometric examination was performed on 37 male patients meeting the DSM-IV criteria for schizophrenia. Thirteen (35.14%) patients had attempted suicide. A non-parametric permutation test was computed to perform the comparability between groups. An analysis of covariance (AnCova) model was constructed with a statistical threshold of $p<0.05$ corrected for multiple comparisons. After controlling for age and severity of illness, results showed significant gray matter density reduction in left superior temporal lobe ($p=0.03$) and left orbitofrontal cortex ($p=0.04$) in patients who had attempted suicide when comparing with non-suicidal patients. Although sample size limitations and potential clinical heterogeneity preclude definitive conclusions, these data point to structural differences in key cerebral areas. Neuroimaging studies are necessary to expand our knowledge of biological mechanisms underlying suicide in schizophrenia.

1. Introduction

Schizophrenia is a severe psychiatric illness affecting almost 1% of the world population (Jablensky, 2003). Its severity depends on both the disability it provokes and the associated suicidal behaviors. Suicide is a devastating outcome for several psychiatric conditions including schizophrenia. Approximately 5% of patients with schizophrenia commit suicide (Palmer et al., 2005) and between 18% and 55% attempt it (Siris, 2001). Suicidal behavior is a pervasive condition which is very hard to prevent in patients with schizophrenia. Although suicide risk in schizophrenia is known to be strongly associated with a history of attempted suicide (Hawton et al., 2005), the scarcity of data about its neurobiological mechanisms and the lack of specificity of the related risk factors limit the implementation of preventive actions. Clinical heterogeneity in the motivations for attempting suicide in these patients may be another difficulty (Aguilar et al., 2003).

Brain imaging has started to yield information about the existence of biological bases of suicide which probably involve prefrontal cortex (PFC) through behavioral impulsivity (Mann, 2005). Ahearn et al. (2001) performed, to our knowledge, the first inter-subject structural magnetic resonance (MR) imaging study centered on suicidal behavior and found that unipolar patients with a history of a suicide attempt had significantly more central gray matter (GM) signal hyperintensities than patients without such history. White matter hyperintensities in psychiatrically hospitalized children and adolescents

Abbreviations: AAL, Automated Anatomical Labeling; BPRS, Brief Psychiatric Rating Scale; CSF, Cerebrospinal Fluid; FDR, False Discovery Rate; GM, Gray Matter; MR, Magnetic Resonance; OFC, Orbitofrontal Cortex; SnPM, Statistical non-Parametric Mapping; STG, Superior Temporal Gyrus; VBM, Voxel-Based Morphometry; WM, White Matter.

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Table 1
Demographic and clinical data from both groups of subjects

	Suicidal patients ($n=13$)	Non-suicidal patients ($n=24$)
Age (years)	37.12 ± 10.02	42.65 ± 10.19
GAF	39.64 ± 11.17	45.09 ± 9.42
BPRS	52.47 ± 11.45	44.58 ± 10.84
Positive PANSS	17.93 ± 5.98	14.91 ± 5.93
Negative PANSS	16.07 ± 6.91	15.83 ± 6.99
Type of antipsychotics		
Typical	14.46%	4.35%
Atypical	42.77%	60.92%
Mixed	42.77%	34.73%

diagnosed of unipolar depression were more frequent in those patients with past suicide attempts compared to a similar subgroup of patients without antecedents of suicidal behaviors (Ehrlich et al., 2004; Ehrlich et al., 2005). Pompili et al. (2007) have recently replicated these findings in a sample of 65 adult psychiatric inpatients with major depressive disorder or bipolar disorder. Finally, another recent study with 17 women with unipolar depression and 17 healthy controls has shown that women with unipolar depression and a history of suicide attempts have smaller right and left orbitofrontal cortex (OFC) grey matter (GM) volumes than healthy women do. These same patients display larger right amygdala volumes than women with unipolar depression who are not suicidal (Monkul et al., 2007). The authors hypothesized that a relatively diminished prefrontal modulation of the anterior limbic network and resulting dysregulation of mood might contribute to poor decision-making and impulsivity in suicide attempters (Monkul et al., 2007). Since the amygdala is also a crucial step in the emotional processing of patients with schizophrenia (Aleman and Kahn, 2005; Brunet-Gouet and Decety, 2006), it could be hypothesized that these prefrontal and amygdalar abnormalities could also occur in suicidal patients with schizophrenia.

Altogether, these studies supply enough background to look for neuroimaging abnormalities in patients with other psychiatric illnesses potentially associated to suicidal behaviors. Although schizophrenia is one of these conditions, no imaging study has evaluated the relationships between brain morphology alterations and suicidal risk in patients with schizophrenia.

Our objective was to investigate, through a whole-brain MR voxel-based morphometry evaluation, the possible structural abnormalities associated with suicidality in patients with schizophrenia. Our main hypothesis was that a history of past suicidal behaviors (attempted suicide) would be associated with localized brain GM structural abnormalities in OFC and amygdala.

2. Material and methods

Our sample included 37 male patients meeting the DSM-IV criteria for schizophrenia. They were part of an on-going study based on the evaluation of the biological bases of auditory hallucinations and emotion in schizophrenia. Patients with and without a history of auditory hallucinations were included. A suicide attempt was defined as any behavior aimed at killing oneself. Suicide attempts were documented through direct questioning of patients and their relatives, and they were then confirmed via chart review. Just before data acquisition, patients were assessed with the Brief Psychiatric Rating Scale (BPRS) (Ventura et al., 1993), the Positive And Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Global Assessment of Functioning (GAF) (Hall, 1995) scales. All patients had the same laterality (all right handed), educational level (all had a secondary school qualification), sex (all males) and ethnic group (all Caucasian). All participants gave written consent for participating in the study, which was approved by the local ethics committee. Table 1 shows clinical and demographical variables.

Images were acquired on a 1.5 T MR scanner (Intera, Philips Medical Systems, Best, The Netherlands). A high-resolution 3D spoiled gradient echo T1-weighted sequence covering the whole-brain (96 axial slices, TR = 7 ms, TE = 1.9 ms, flip angle = 8°, acquisition matrix = 256 × 256, field of view = 220 mm and 1.25 mm slice thickness with no inter-slice gap) was acquired with a voxel size of 0.86 × 0.86 × 1.25 mm.

Data processing was done with the SPM5 software (Statistical Parametric Mapping 5, Welcome Department of Cognitive Neurology, FIL, London, UK). Images were analyzed using the optimized Voxel-Based Morphometry (VBM) method (Ashburner, Friston, 2000; Good et al., 2001). Custom templates were created to minimize errors due to differences in the contrast of the images and specific non-uniformities of the signal in the MR images, and demographical differences in the sample. Each original T1-weighted MR image was normalized with the whole-brain custom template. In addition, these normalized images were interpolated to voxel dimensions of 1 × 1 × 1 mm. After removing the scalp, skull and dural venous sinus, non-linear spatial normalization parameters between GM template and GM maps were applied to transform the T1 raw images. The reconstructed images were segmented and smoothed by a Gaussian kernel obtaining GM, white matter and cerebrospinal fluid maps.

Data were analyzed with a non-parametric approach, which is suitable for analyses with low degrees of freedom. Non-parametric permutation testing provides a flexible and intuitive methodology for neuroimaging statistics. Furthermore, it successfully accounts for the multiple comparison problem implicit in the standard voxel-by-voxel hypothesis testing framework. Statistical non-Parametric Mapping (SnPM) (Nichols and Holmes, 2002) was used to perform a voxel-wise comparison of GM density of patients with and without suicide attempts. An analysis of covariance (AnCova) model was constructed, including a group condition (suicidal patients and non-suicidal patients) and two nuisance variables (age and BPRS total score). The model was estimated against 30,000 permutations.

Results where thresholded at $p<0.05$ corrected for multiple comparisons following a False Discovery Rate methodology (Genovese et al., 2002). A spatial threshold filter was also applied to report only clusters with a minimum size of 83 voxels (expected numbers of voxels per cluster). Statistically significant areas were labeled with the Automated Anatomical Labeling (AAL) software (Tzourio-Mazoyer et al., 2002). Coordinates for identifying each area were determined by the maximum Student t value in the corresponding area.

3. Results

Thirteen (35.14%) patients had attempted suicide. No significant differences in the duration of illness or type of treatment existed between these patients and patients without antecedents of suicide attempts (controls), but Mann–Whitney tests revealed that attempters were significantly younger (37.12 ± 11.02 vs. 42.65 ± 10.19; $p<0.05$) and exhibited greater illness severity as indicated by BPRS scores (52.47 ± 11.45 vs. 44.58 ± 10.84) than controls. Attempters had performed an average of 2.3 suicide attempts (range 1–4).

After controlling for age and severity of illness, significant ($p<0.05$ FDR corrected) GM density reductions in the left OFC ($p=0.04$) and left

Table 2
Areas with GM density reductions in schizophrenic patients with a history of suicide attempts ($p<0.05$ FDR corrected $k=83$)

Coordinate (mm)			Label	Left/Right	T value	$p_{corrected}$	Brodmann area
X	Y	Z					
−40	−31	11	Temporal Superior	Left	5.13	0.03	42
−9	39	−21	Frontal Superior Orbital	Left	4.90	0.04	11

Corrected p values are given at cluster level.

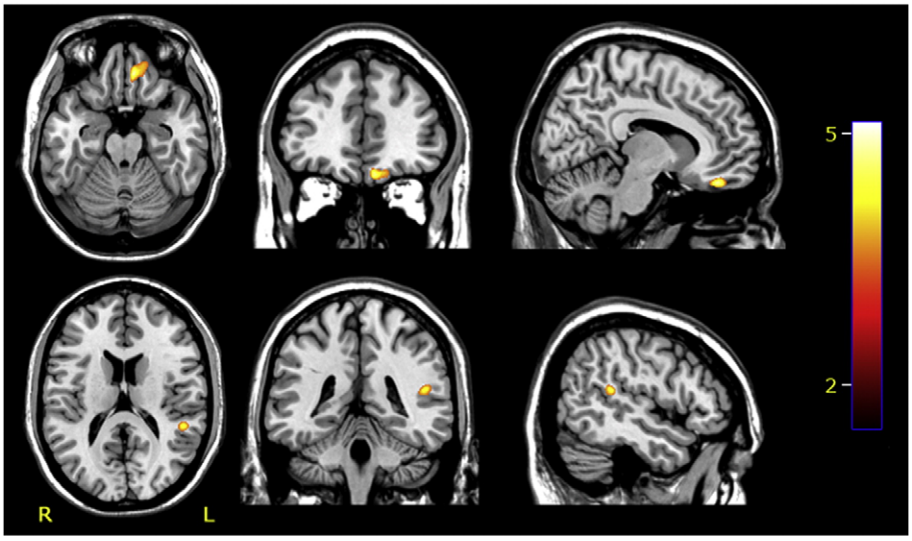

Fig. 1. Areas with GM density reductions in schizophrenic patients with a history of suicide attempts ($p<0.05$ FDR corrected, $k=83$).

superior temporal gyrus (STG) ($p=0.03$) were found in patients who had previously attempted suicide (Table 2, Fig. 1).

4. Discussion

This study has demonstrated GM density reductions in the left OFC and left STG in schizophrenic patients who had previously attempted suicide compared to similar patients without antecedents of suicidal behaviors.

This is the first morphometric study on schizophrenic patients' suicidality. A tentative rationale for these findings based on our knowledge of suicide biological mechanisms can be given. First, less dense OFC may have prompted these patients to a greater impulsivity which could have precipitated their suicidal attempts. OFC plays an important role in inhibition of inappropriate responses, decision-making and impulsiveness (Berlin et al., 2004; Kertzman et al., 2006) which are potentially linked to suicidal behavior. In particular, impulsivity has been associated with increased suicidal risk in patients with schizophrenia (Hawton et al., 2005). However, data are not completely concordant about this subject. The association between suicidality and impulsivity is based on indirect data (Fenton, 2000; Kreyenbuhl et al., 2002) and the results of only two studies in a review by Hawton et al. (2005). Moreover, a recent psychological autopsy study with completed suicides has failed to replicate this association (McGirr et al., 2006).

Our second finding is intriguing. We found smaller left STG in our suicidal patients. Since we controlled for illness severity and age, this finding could be related to other pathogenic features. Left STG is one of the most consistently reported abnormal regions in schizophrenia (Honea et al., 2005) and it has been associated to the presence and severity of auditory hallucinations (see García-Martí et al., 2008). Mechanisms for attempting suicide probably include the distress in response to hallucinations and delusions (Fialko et al., 2006). On the other hand, Martí-Bonmatí et al. (2007) have recently shown how functional overactivation associated with auditory emotional stimuli coexisted in a large brain cluster with left STG density reductions in schizophrenic patients with chronic auditory hallucinations. The mentioned auditory stimuli were introduced by means of an auditory paradigm that was developed to study the emotional response to auditory stimuli consisting of voices usually heard by patients with schizophrenia (Sanjuán et al., 2007). Taken together, these findings suggest a role for the left STG in the emotional dysfunction associated to auditory hallucinations.

Notwithstanding, and in contrast with Monkul et al.'s study (2007), we did not find significant differences in amygdalar volumes. They found larger right amygdale in suicidal patients with major depression. Several explanations can be given for these discordant results. Differential neurobiological mechanisms for suicidal behaviors may be operating in depressive disorders and schizophrenia. Moreover, suicidal patients with schizophrenia probably comprise a more heterogeneous group in regard with their biological mechanisms for attempting suicide compared with depressive patients. In support of this affirmation from a clinical background, some data indicate that there may be at least two subgroups of patients with schizophrenia regarding their suicidal motivation (Aguilar et al., 2003; Acosta et al., 2006). Since our sample was not a large sample and several biases may be influencing results, a type II error cannot be ruled out. Differences in amygdalar volumes (either enlargements or reductions) have been reported in patients with schizophrenia as compared to healthy subjects. Potential biases that are relevant for our study include antipsychotic treatment, illness subtype, chronicity of the illness and gender (Shayegan and Stahl, 2005). Monkul et al.'s study (2007) used a smaller sample (seven suicidal unipolar patients, 10 non-suicidal unipolar patients and 17 healthy comparison subjects) with a region of interest approach. Finally, while they only included female patients in their study our sample was comprised of male patients. Sex effects on brain structure could also have influenced results in both studies. In fact, a very recent study on patients with schizophrenia or bipolar disorder has shown diagnosis-by-sex interactions in amygdalar and hippocampal volumes (Frazier et al., 2008).

This study has some limitations that should be mentioned. First, results from this study only apply to male patients with schizophrenia. Second, MRI and clinical data at the moment of the suicide attempt were not available. Third, suicidal attempters were younger than non-suicidal attempters. Global grey matter volume decreases linearly with age in the whole population (Good et al., 2001). In our opinion, we can discard a major age effect bias since we would have expected the opposite effect (increase of GM density) in our subgroup of suicidal patients. Finally, this study is partly limited by the absence of healthy comparison subjects. Although the control group is suited for the purpose of this study, since these patients share similar characteristics with those patients in the case group and differ on the condition under study, suicidal mechanisms not related to pathological conditions such as depression and schizophrenia remain not ascertained. Further studies with a larger sample and more profound clinical evaluation (including neuropsychological data) are required to test key hypotheses deriving from these results.

5. Conclusion

This is the first study to investigate structural changes associated to suicidal behaviors in patients with schizophrenia. Our results showed structural differences in key cerebral areas, namely, significantly GM volume reductions associated to antecedents of suicide attempts in left OFC and left STG. However, we could not demonstrate significant differences between groups for amygdala volumes, in contrast with our hypothesis.

More neuroimaging studies in larger populations with a clearly defined clinical phenotype are necessary to expand our knowledge of the biological mechanisms underlying suicide in schizophrenia.

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