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Review article

Dysfunction of neural circuitry in depressive patients with suicidal behaviors: A review of structural and functional neuroimaging studies

Huawei Zhang [a], Ziqi Chen [a], Zhiyun Jia [a,b,*], Qiyong Gong [a,**]

[a] Huaxi MR Research Center (HMRRC), Department of Radiology, West China Hospital of Sichuan University, Chengdu, PR China
[b] Department of Nuclear Medicine, West China Hospital of Sichuan University, Chengdu, PR China

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ABSTRACT

Suicide is an important public problem. Understanding the neurobiological mechanisms of suicidal behavior in depression will facilitate the development of more effective prevention strategies for suicide. There are several reviews of imaging studies of suicidal behavior, but none of these reviews have focused only on suicide in depression. We reviewed neuroimaging studies of suicide in depression in recent years. The majority of studies found structural and functional alterations in the orbital frontal cortex, anterior cingulate cortex and striatum in depressive patients with suicidal behaviors. The evidence suggests that the frontal–striatal circuitry, which includes the striatum, orbital frontal and anterior cingulate cortices, is involved in the neurobiology of suicide in depressive patients. These findings also indicate that not all suicides have the same underlying neuropathology. Future studies require larger samples and more accurate subtypes of suicide. Furthermore, combining neuroimaging and other new technologies in molecular biology will be helpful to reveal the pathogenesis of suicidal behavior in depression.

Contents

Abbreviations: ACC, anterior cingulate cortex; ALIC, anterior limb of the internal capsule; ATT(s), suicide attempter(s); BIS, Barratt Impulsivity Scale; CMS, cortical midline structures; DTI, diffusion tensor imaging; FA, fractional anisotropy; GM, gray matter; HC(s), healthy control(s); MDD, major depressive disorder; MRI, magnetic resonance imaging; NAT(s), depressed people without suicide attempt(s); OFC, orbital frontal cortex; PET, positron emission tomography; PFC, prefrontal cortex; (r)CBF, (regional) cerebral blood flow; SA(s), suicide attempt(s); SPECT, single photon emission computed tomography; VBM, voxel-based morphometry; WM, white matter; WML, white matter brain lesion.

* Correspondence to: Z. Jia, Huaxi MR Research Center (HMRRC), Department of Radiology, West China Hospital, Sichuan University, No. 37 Guo Xue Xiang, Chengdu, Sichuan 610041, PR China. Tel.: +86 13408419087; fax: +86 28 85423503.
** Correspondence to: Q. Gong, Tel./fax: +86 28 85423503.
E-mail addresses: zhiyunjia@hotmail.com (Z. Jia), qiyonggong@hmrrc.org.cn (Q. Gong).

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1. Introduction

Suicidality is a serious public health problem, and approximately one million individuals worldwide die from suicide each year. The World Health Organization reported that suicide is among the three leading causes of death among individuals aged 15–44 years in some countries and the second leading cause of death among those 10–24 years of age; these figures do not include suicide attempts, which can be many times more frequent than suicide. Self-inflicted injuries, including suicide attempts represented 1.4% of the global burden of disease in 2002 and are expected to increase to 2.4% in 2020 (Bertolote et al., 2005).

The suicide risk is much higher in individuals with psychiatric disorders. More than 90% of suicide victims and attempters have at least one current axis I major psychiatric disorder (mainly untreated), the most frequent of which is major depressive episodes (59–87%) (Rihmer et al., 2002). Depression is one of the most powerful clinical predictors of suicide, and mixed states of depression could also be an important forerunner of suicidal behavior (Rihmer, 2007). A large-scale, follow-up study of major depressive patients without other axis I psychiatric disorders showed that 4.2% of patients died from suicide (Coryell and Young, 2005). As suicide is a major cause of years of life lost, its prevention and prediction are receiving increasing attention. Despite the multiple factors associated with suicide, an adequate approach for predicting future suicidal behavior remains to be explored. Currently, suicide history and future suicide risk are often assessed via an interview and suicide risk scales, such as the Suicide Intent Scale (Gorlyn et al., 2013) and the Columbia-Suicide Severity Rating Scale (Posner et al., 2011). However, it is difficult to obtain sufficient information when patients are unwilling or unable to share subjective experiences with clinicians. Recent neurobiological studies of suicide may provide some objective indicators for suicide prediction. Many studies examining neurobiology of suicidal behavior have focused on the role of serotonergic abnormalities in psychiatric patients with histories of suicidal acts or on postmortem studies of suicide victims (Asellus et al., 2010; Gos and Jankowski, 2012; Mann and Currier, 2010; Spreux-Varoquaux et al., 2001). There is strong evidence for a relationship between low levels of 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid (CSF) and suicidal behavior (Asberg et al., 1976; Lee and Kim, 2011; Maris, 2002). A meta-analysis confirmed that low CSF 5-HIAA had some predictive power with respect to completed suicide in mood disorders (Mann et al., 2006). However, traditional methods of neurochemistry do not provide information about the anatomical location of abnormalities in vivo. Brain imaging techniques, such as MRI, PET and SPECT, are promising tools that can provide non-invasive or minimally invasive dynamic measurements of the physiological functions or structural brain abnormalities in vivo. For example, one SPECT study of suicidal behavior has shown that depressed patients who attempted suicide had greater regional cerebral blood flow (rCBF) at rest in the right insular cortex, the dorsal anterior cingulate gyrus and the inferior parietal lobule compared to non-suicidal depressed patients (Amen et al., 2009).

To understand the neurobiological mechanisms of suicidal behavior, there are two reviews of imaging studies of suicidal behavior (Desmyter et al., 2011; van Heeringen et al., 2011), but neither of these reviews has focused only on suicide in depression. The results in previous neuroimaging studies on suicide have varied widely. Some scholars have suggested that one possible explanation for the differences between studies was that there may be different mechanisms leading to the vulnerability to suicide in different populations (Underwood and Arango, 2011), and we suspect that different psychiatric disorders may be one of the potential factors. To date, no study has compared suicidal behavior in patients with different psychiatric disorders, but there is evidence that the clinical characteristics of suicidal behavior are not the same in patients with different psychiatric disorders (Nakagawa et al., 2011). We believe that the neurobiology underlying suicide in depression is different from that in other psychiatric disorders. The PubMed, Scopus, and Medline databases were comprehensively searched using "suicide", "suicidal", "depression", "depressive disorder", "imaging", "computed tomography", "magnetic resonance imaging", "positron emission tomography", "single photon emission computed tomography", "functional magnetic resonance imaging", "diffusion tensor imaging", "CT", "MRI", "PET", "SPECT", and "DTI" as keywords. Additionally, the reference lists of the identified studies were checked for additional publications matching the inclusion criteria. We used relatively strict inclusion criteria to ensure the quality of the articles. The inclusion of studies in this review was based on the following criteria: 1) studies must contain certain sample size, case reports were excluded; 2) studies were required to include groups composed of individuals with histories of suicide attempts and without such histories; 3) studies were included only if the patients were with mood disorders (only unipolar but not bipolar disorders); and 4) the imaging techniques employed should include CT, MRI, PET, SPECT or fMRI. Studies in patients with suicidal ideation or patients with future suicidal behavior are not included in this review. Studies of patients with comorbidities such as borderline personality disorder and attention-deficit/hyperactivity disorder are excluded from this review. Studies of white matter hyperintensities in patients with suicidal behavior were not included in this review, because the method of indentifying the hyperintensity was not such objective. The strategy we adopted to identify the papers included in this review is shown in Fig. 1.

2. Brain regions associated with suicidal behavior in depressive patients

2.1. Orbital frontal cortex

Despite the heterogeneous results, the orbital frontal cortex (OFC) was the most frequently identified brain region in studies of suicide in depression. The OFC, a sub-region of the prefrontal cortex, is involved in emotional and cognitive processes, such as decision-making and the valuation of actions and stimuli (Salzman and Fusi, 2010). Abnormalities in the OFC in depressive patients are widely reported in neuroimaging studies (Arnone et al., 2012; Groenewold et al., 2013; Liao et al., 2013). Several studies have drawn attention to the relationship between OFC abnormalities and impairments in decision-making in suicidal behavior (Jollant et al., 2008, 2010; Monkul et al., 2007). Jollant et al. were the first to report a specific impairment in decision-making in SAs. They found that SAs but not non-attempters achieved lower scores in a decision-making task than HCs, suggesting that the decision-making impairment was associated with the susceptibility to suicidal behavior rather than the susceptibility to depression (Jollant et al., 2005). In their subsequent fMRI study, compared to NATs, ATTs performed worse in a decision-making task and had decreased activation during risky versus safe choices in the left lateral OFC (Jollant et al., 2008). A PET study by Leyton et al. (2006) detected that SAs had reduced normalized α-[11C] methyl-L-tryptophan trapping in the OFC and the ventral medial prefrontal cortices compared to HCs. Furthermore, a negative correlation was noted between suicide intention and α-[11C] methyl-L-tryptophan trapping in these regions. A recent structural study found reduced GM volume in the OFC. The authors argued that the OFC is crucial for changing behavior when facing unexpected outcomes, when subjects must change an established behavioral response in order to adapt to new contingencies (Benedetti et al., 2011). There is also evidence that impulsivity can emerge after brain injuries to the OFC and the adjacent white matter (Berlin et al., 2004), which is consistent with the finding that decreased gray matter volume in the OFC is associated with high impulsivity (Matsuo et al., 2009). Taken together, abnormalities in the OFC may result in a dysfunction of emotional regulation which can contribute to impairments in decision making and impulsivity as susceptibility to suicidal behavior in depressive patients.