Journal of Affective Disorders 188 (2015) 202–209

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

Control-related frontal-striatal function is associated with past suicidal ideation and behavior in patients with recent-onset psychotic major mood disorders

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ARTICLE INFO

Article history:
Received 15 June 2015
Received in revised form
16 August 2015
Accepted 21 August 2015
Available online 3 September 2015

Keywords:
Bipolar I disorder
Major depressive disorder
Psychosis
Suicide risk
Cognitive control
Frontal cortex

ABSTRACT

Objective: Suicide is highly-prevalent in major mood disorders, yet it remains unclear how suicidal ideation and suicidal behavior relate to brain functions, especially those that support control processes. We evaluated how prefrontal cortex (PFC) activity during goal-representation (an important component of cognitive control) relates to past suicidal ideation and behavior in patients with psychotic major mood disorders.

Method: 30 patients with recent-onset of either DSM-IV-TR-defined bipolar disorder type I ($n=21$) or major depressive disorder ($n=9$) with psychotic features, but neither in a major mood episode nor acutely psychotic at study, were evaluated for past suicidal ideation and behavior (Columbia Suicide Severity Rating Scale) and functional MRI during cognitive control task performance. Group-level regression models of brain activation accounted for current depression, psychosis and trait impulsivity.

Results: Intensity of past suicidal ideation was associated with higher control-related activation in right-hemisphere regions including the ventrolateral PFC (VLPFC) and orbitofrontal cortex, rostral insula, and dorsal striatum. Among those with past suicidal ideation ($n=16$), past suicidal behavior ($n=8$) was associated with higher control-related activation in right-hemisphere regions including VLPFC, rostrolateral PFC, and frontal operculum/rostral insula; and relatively lower activity in midline parietal regions, including cuneus and precuneus.

Limitations: The sample size of subjects with past suicidal behavior was modest, and all subjects were taking psychotropic medication.

Conclusions: This study provides unique evidence that in early-course psychotic major mood disorders, suicidal ideation and behavior histories directly relate to PFC-based circuit function in support of cognitive control.

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1. Introduction

Suicide is a major public health problem worldwide. It is a leading cause of death, and one of the most common causes of death for young people, including young adults (Hawton and van Heeringen, 2009; Nock et al., 2008), and suicide confers an enormous public health impact (Goldsmith and Institute of Medicine, 2002). In patients with major mood disorders (major depressive disorder, MDD, and bipolar affective disorder type I, BP1), suicide is the leading cause of premature death, and those who are relatively younger or early in the course of illness are at particularly high risk for suicidal behavior (Hawton and van Heeringen, 2009; Nock et al., 2008; Oquendo et al., 2005), though suicide risk can remain elevated for many years after a single suicide attempt among patients with recent-onset psychotic disorders (Dutta et al., 2010).

Despite the increasing attention to clinical risk factors for suicide, how brain dysfunction confers this risk remains unclear. Serotonergic disturbances in the lateral and medial prefrontal cortex (PFC) are observed in post-mortem studies of suicide victims (reviewed in (Mann, 2003)). It remains unclear whether these

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http://dx.doi.org/10.1016/j.jad.2015.08.049
0165-0327/Published by Elsevier B.V.

are independent of co-morbid depression or psychiatric diagnosis *per se*. While patients with major mood disorders have well-established disturbances in PFC and subcortical function (Chen et al., 2011), there is also an expanding literature evaluating *in vivo* correlates of suicidal behavior in major mood disorders, which indicates disturbances in structure and function of PFC, relative to mood disorder patients lacking this history (reviewed in Zhang et al., 2014). In adults with MDD, this includes white matter disturbances in right PFC and striatum (Jia et al., 2010), left orbitofrontal cortex (OFC) and thalamus (Jia et al., 2014), and dorsomedial PFC (Olvet et al., 2014); gray matter decreases in caudate and anterior cingulate cortex (ACC) (Wagner et al., 2011), and in frontoparietal regions, plus insula, caudate and other subcortical regions (Hwang et al., 2010); in late-life MDD, lower putamen gray matter (Dombrovski et al., 2012), and in BP1, white matter disturbances in left OFC (Mahon et al., 2012). fMRI studies of brain function have found suicidal behavior associated with relatively greater responses to angry faces in ACC and dorsolateral PFC (DLPFC) in depressed adolescents (Pan et al., 2013) as well as in right lateral OFC in euthymic adult MDD patients (Jollant et al., 2008), and relatively lower activity in right ACC during response inhibition (Pan et al., 2011). Euthymic MDD patients with a history of suicidal behavior also exhibit lower responses to risky choices on the Iowa Gambling Task in left lateral OFC (Jollant et al., 2010), and among late-life MDD patients, lower ventromedial PFC responses to expected rewards (Dombrovski et al., 2013). More diagnostically-heterogeneous populations with past suicide attempts also show functional disturbances in medial and lateral PFC sectors during varied cognitive tasks (Amen et al., 2009; Audenaert et al., 2002; Reisch et al., 2010). Taken together, these studies suggest that mood disorder patients with suicidal behavior exhibit altered structure and function of PFC-based circuits during complex cognition, which may be altered over and above those patients who share other clinical features (e.g. diagnosis or other symptoms) yet lack histories of suicide attempts.

Nonetheless, it remains unclear how disrupted PFC-based circuit operation contributes to suicide risk in these populations. In this context, models of PFC function derived from cognitive neuroscience offer an emerging framework to study these clinical phenomena. These models generally posit superordinate *control processes*, which support cognitive processes as diverse as attention, decision-making, thought/language, emotion-regulation and action (Koechlin et al., 2003; Miller and Cohen, 2001). The DLPFC subserves goal-representation as a pillar of control, via the encoding and use of rules or strategies for decision-making, while more rostral PFC regions support high-level organization/integration of multiple subprocesses, such as those required for prospective memory and meta-cognition (Dumontheil et al., 2008; Fleming and Dolan, 2012), and ventrolateral PFC (VLPFC) regions support action selection and inhibitory control (Aron, 2007; Levy and Wagner, 2011). The PFC thereby biases processing of attention, perception and action, to influence context-appropriate, goal-oriented motor output via striato-thalamic circuits to maximize goal-attainment (Koechlin et al., 2003; Miller and Cohen, 2001). Considering that cognitive control performance is associated with serotonergic gene variation (Strobel et al., 2007), frontal-based control processes may link serotonergic dysfunction to suicidal behavior. PFC-based cognitive control disturbances may therefore represent an important mechanism underlying suicide risk.

In an earlier study of recent-onset schizophrenia patients (Minzenberg et al., 2014), we found that a history of suicidal ideation was associated with relatively lower control-related PFC activity, and among those who reported past suicidal ideation, suicidal behavior was associated with relatively lower control-related activation in premotor cortex ipsilateral to the active primary motor cortex. One important issue in this literature (and more generally in clinical neuroscience) is whether the relationships found between brain function and behavior are diagnostically-specific, or rather are general brain-behavior relationships that are invariant across diagnoses (Cuthbert and Insel, 2010). In order to test our model of control-related PFC function as a correlate of suicidal behavior in major mood disorders, and to address the question of diagnostic specificity, we tested recent-onset patients with psychotic major mood disorders (unipolar depression or bipolar 1), using a study design that is identical to that employed in our study of recent-onset schizophrenia patients (Minzenberg et al., 2014). Compared to the schizophrenia patients, the mood disorder patients were enrolled from the same first-episode psychosis clinic, evaluated clinically in an identical manner, including the same symptom measures and long-term suicide risk assessment (Columbia Suicide Severity Rating Scale; (Posner et al., 2011)), and underwent the same fMRI protocol and analytic procedures. As with the prior study, our neuroimaging analyses accounted for major symptom domains previously identified as clinical risk factors for suicide in these populations, including depression, psychosis and impulsivity (Minzenberg et al., 2014). This allowed tests of the direct relationships of frontal circuit function to past suicidal ideation and behavior which are not simply accounted for by these clinical risk factors. Furthermore, in the model relating past suicidal behavior to brain function, we analyzed only those subjects who were positive for past suicidal ideation, allowing us to potentially disambiguate brain function associated with overt behavior from that associated with ideation, an important yet under-recognized issue in suicide-risk research (Klonsky and May, 2014).

2. Experimental/materials and methods

2.1. Subjects

The study was conducted at the Imaging Research Center at the University of California–Davis Medical Center. All procedures were approved by the UC Davis School of Medicine Institutional Review Board. Inclusion criteria included age 18–50 years, right-handedness (by Edinburgh Handedness Inventory), and diagnosis of 296.X with past psychotic episode (by DSM-IV-TR). Exclusion criteria included neurological illness (including head injury with loss of consciousness), uncorrectable visual problems or peripheral motor disturbance, full-scale IQ < 80 (by 2-scale Wechsler Abbreviated Scale of Intelligence), co-morbid 295.X diagnosis, active substance abuse or dependence in the 6 months prior to study, a history of self-harm with neurological sequelae, significant uncontrolled medical illness, and known incompatibility with MRI procedures. All included subjects tested negative for illicit drugs in the urine at all study visits. After complete description of the study to the subjects, written informed consent was obtained.

All patients were recruited from the UCD Early Diagnosis and Preventive Treatment (of Psychosis) research clinic, as clinically-stable outpatients, with onset of psychotic symptoms within 2 years of study, and no hospitalizations or changes in medication regimen for at least two months prior to study. All reported past suicidal behaviors occurred during a major mood episode, however, none were in a major mood episode nor acutely psychotic at study. The sample included patients with BP1 ($n=21$) and major depressive disorder ($n=9$). The frequencies of prescribed medications at study were atypical antipsychotics ($n=17$); lithium ($n=5$); anticonvulsants ($n=3$); antidepressants ($n=7$). None were receiving clozapine or psychotherapies specifically targeting suicide risk. Patients were assessed with the Structured Clinical Interview for DSM-IV-TR. Diagnosticians were masters/doctoral-level, SCID-trained clinicians, with demonstrated reliability, defined