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Frontal cortex control dysfunction related to long-term suicide risk in recent-onset schizophrenia

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ABSTRACT

Objective: Suicide is highly-prevalent and the most serious outcome in schizophrenia, yet the disturbances in neural system functions that confer suicide risk remain obscure. Circuits operated by the prefrontal cortex (PFC) are altered in psychotic disorders, and various PFC changes are observed in post-mortem studies of completed suicide. We tested whether PFC activity during goal-representation (an important component of cognitive control) relates to long-term suicide risk in recent-onset schizophrenia.
Method: 35 patients with recent-onset of DSM-IV-TR-defined schizophrenia (SZ) were evaluated for long-term suicide risk (using the Columbia Suicide Severity Rating Scale) and functional MRI during cognitive control task performance. Group-level regression models associating control-related brain activation with suicide risk controlled for depression, psychosis and impulsivity.
Results: Within this group, past suicidal ideation was associated with lower activation with goal-representation demands in multiple PFC sectors. Among those with past suicidal ideation (n = 18), reported suicidal behavior was associated with lower control-related activation in premotor cortex ipsilateral to the active primary motor cortex.
Conclusions: This study provides unique evidence that suicide risk directly relates to PFC-based circuit dysfunction during goal-representation, in a major mental illness with significant suicide rates. Among those with suicidal ideation, the overt expression in suicidal behavior may stem from impairments in premotor cortex support of action-planning as an expression of control. Further work should address how PFC-based control function changes with risk over time, whether this brain–behavior relationship is specific to schizophrenia, and address its potential utility as a biomarker for interventions to mitigate suicide risk.

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1. Introduction

Suicide is a major public health problem worldwide. It is a leading cause of death, among the most common causes of death for young people, including young adults (Nock et al., 2008; Hawton and van Heeringen, 2009), and confers an enormous public health impact (United States. Public Health Service: Office of the Surgeon General., 1999; United States. Public Health Service, 2001; Goldsmith et al., 2002). In schizophrenia, the risk for suicidal ideation, behavior and completed suicide is particularly high early in the illness course (Dutta et al., 2010; Pompili et al., 2011; Nielssen et al., 2012), though suicide risk remains elevated for many years after a single suicide attempt (Dutta et al., 2010).

Despite the increasing attention to clinical risk factors for suicide, how brain dysfunction confers this risk remains unclear. Post-mortem studies of suicide victims reveal many serotonergic disturbances in the lateral and medial PFC (reviewed in Mann, 2003). These findings are generally independent of co-morbid depression history, or psychiatric diagnosis per se. These studies suggest that the lateral and medial PFC are key loci of serotonergic dysfunction associated with suicide.

Nonetheless, it remains unclear how disrupted PFC-based circuit operation contributes to suicide risk in at-risk populations. The major

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cognitive neuroscience models of PFC function generally posit superordinate *control processes*, which support cognitive processes as diverse as attention, behavior, decision-making, thought/language, and emotion-regulation. These models include a role for lateral PFC subregions (especially dorsolateral PFC, or DLPFC) in goal-representation via the encoding and use of rules or strategies for decision-making, thereby biasing processing of attention, perception and action, to influence motor output via striato-thalamic circuits (Miller and Cohen, 2001; Koechlin et al., 2003). In contrast, the posterior medial PFC monitors conflict between goals and tasks (Botvinick et al., 2001) and other mismatches between the individual's status and goals, such as negative affect and pain (Schackman et al., 2011). In these conditions, the medial PFC signals to the DLPFC the need to bolster control to optimize goal attainment.

Other closely-linked frontal cortical regions represent goal-relevant information, including rostral PFC, which represents hierarchical aspects of complex rules and actions (Badre, 2008); and rostral medial PFC sectors (e.g. dorsomedial and ventromedial PFC), which represent self-referential aspects and valuate environmental stimuli. Disturbances in elements of these interacting networks may then manifest clinically as disturbances of the control of thought, behavior or emotion, observed as suicidal ideation or behavior. Considering that cognitive control performance is associated with serotonergic gene variation (Strobel et al., 2007), frontal-based control processes may link serotonergic dysfunction to suicide.

PFC-based cognitive control disturbances may therefore represent an important mechanism underlying suicide risk. Cognitive control-related medial and lateral PFC dysfunction is well-established in schizophrenia (Minzenberg et al., 2009; Lesh et al., 2011, 2013), including in the first-episode (Yoon et al., 2008). Schizophrenia outpatients with past suicide attempts also have increased volumes of inferior PFC white matter relative to those without suicide attempts (Rusch et al., 2008), as well as decreased orbitofrontal gray matter density (Aguilar et al., 2008), and relatively higher-risk schizophrenia patients exhibit altered effective connectivity between the left-hemisphere posterior cingulate cortex and medial PFC, relative to lower-risk patients and healthy controls (Zhang et al., 2013). Schizophrenia patients with past suicide attempts also have increased right amygdala volume (Spoletini et al., 2011), which could in principle be associated with altered ascending influence on PFC circuit function. In addition, decreased fractional anisotropy in the cingulum bundle is observed in suicidal traumatic brain-injured patients (Yurgelun-Todd et al., 2011). More diagnostically-heterogeneous populations with past suicide attempts show functional disturbances in medial and lateral PFC sectors during varied cognitive tasks (Audenaert et al., 2002; Amen et al., 2009; Jollant et al., 2010; Reisch et al., 2010). These studies, while preliminary, suggest that patients with suicidal behavior exhibit dysfunction of PFC-based circuits during complex cognition, and may be impaired over and above those patients who share other clinical features (e.g. diagnosis or other symptoms).

We therefore tested the hypothesis that PFC-based circuit function with explicit control demands directly relates to suicide risk, in schizophrenia patients who are early in the illness course, when this risk is particularly elevated. We employed an emerging clinical standard for suicide risk assessment, the Columbia Suicide Severity Rating Scale (Posner et al., 2011). Critically, in the analyses we accounted for major symptom domains previously identified as clinical risk factors for suicide in schizophrenia, including depression, psychosis and impulsivity. This allowed tests of the direct relationships of frontal circuit dysfunction to suicide risk, which are not simply accounted for by these clinical risk factors. Additionally, in the model of past suicidal behavior to brain dysfunction, 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.

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 295.X (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 Wechsler Abbreviated Scale of Intelligence), active substance abuse or dependence in the 6 months prior to study, significant uncontrolled medical illness, and previously-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. The frequencies of prescribed medications at study were antipsychotics (n = 32), anticonvulsants (n = 4) and antidepressants (n = 6). None were receiving lithium or clozapine. Patients were assessed with the Structured Clinical Interview for DSM-IV-TR. Diagnosticians were masters/doctoral-level, SCID-trained clinicians, with demonstrated reliability, defined by ≥.80 intraclass correlation-coefficient (ICC) for continuous measures and kappa ≥ .70 for categorical measures. All diagnoses were confirmed via consensus conference, and monthly reliability interviews to prevent drift. Based upon 10 sessions during the course of this study, diagnostic reliability for the SCID was kappa ≥ 0.8, and for symptom total scores ICCs were ≥0.76. A subset of the present sample was previously reported for AX-CPT task-related fMRI effects compared to a healthy comparison group (not focused on suicide risk), in Lesh et al. (2013). The present study represents a secondary analysis drawn from a subset of that sample, to specifically test relationships of brain function to suicide risk.

2.2. Clinical measures

2.2.1. Clinical measure of suicide risk — description and rationale

Suicide risk was rated with the Columbia Scale for the Rating of Suicide Severity (C-SSRS), a relatively brief, yet comprehensive, structured interview-based instrument with good validity and internal reliability in 3 multi-site studies with diverse clinical populations (Posner et al., 2011). This scale is comprised of three subscales. Suicidal Ideation (SI) is an ordinal subscale containing items including the wish to be dead, the specificity of these thoughts, including whether they are "active", with intent and plan. Intensity of Ideation (II) considers the frequency, duration, controllability, deterrents and reasons for thoughts of suicide. Suicidal Behavior (SB) is a nominal subscale that categorizes past actual, interrupted and aborted attempts to die, and preparatory acts, and for actual attempts, the potential or actual lethality or medical damage sustained in the attempt(s). Items on each subscale are associated with future suicidal behavior and/or completed suicide (Posner et al., 2011). SI items are rated on a yes/no basis, II items on a 1–5 scale, and SB as yes/no, with counts of actual, interrupted and aborted attempts.

We used the following criteria to stratify patients in each group on each of the two non-continuous C-SSRS subscales (SI and SB): for SI, the presence of any past suicidal ideation (i.e. positive on any SI item), versus no past suicidal ideation; and for SB, the presence of any past behavior that can be considered the *initiation* of deliberate self-harm with intent to die as the critical discrete threshold (i.e., a positive response to actual attempt, interrupted attempt, or aborted attempt). For SB, we considered positive responses that were restricted to Non-Suicidal