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Self-harm in schizophrenia is associated with dorsolateral prefrontal and posterior cingulate activity

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ABSTRACT

Self-harm, such as self-cutting, self-poisoning or jumping from height, regardless of intentions, is common among people with schizophrenia. We wished to investigate brain activations relating to self-harm, in order to test whether these activations could differentiate between schizophrenia patients with self-harm and those without. We used event-related functional MRI with a go/no-go response inhibition paradigm. Fourteen schizophrenia patients with a history of self-harm were compared with 14 schizophrenia patients without a history of self-harm and 17 healthy control participants. In addition, we used standard clinical measures and neuropsychological tests to assess risk factors associated with self-harm. The right dorsolateral prefrontal cortex (DLPFC) and the left posterior cingulate cortex differentiated all three groups; brain activation in these regions being greatest in the control group, and the self-harm patient group being greater than in the non-self-harm patient group. In the self-harm patient group, right DLPFC activity was positively correlated with severity of suicidal thinking. In addition, both patient groups showed less activation in the right orbitofrontal cortex, left ventral anterior cingulate cortex and right thalamus. This is the first study to report right DLPFC activation in association with self-harm and suicidal thinking in patients with schizophrenia. This area could be a target for future neuromodulation studies to treat suicidal thinking and self-harm behaviors in patients with schizophrenia.

1. Introduction

Self-harm is a significant risk factor for later completed suicide: previous self-harm carries an eightfold increase for completed suicide in patients with schizophrenia. Systematic reviews have indicated that clinical features associated with suicide in patients with schizophrenia include depressive episodes, previous suicide attempts, and substance abuse (Hawton et al., 2005; Hor and Taylor, 2010). Other risk factors associated with suicide attempts included high impulsivity, relatively preserved executive cognitive functions, and good insight into their illness (Kim et al., 2003). Iancu and colleagues have highlighted the importance of impulsivity associated with suicide attempts and ideation in patients with schizophrenia (Iancu et al., 2010). They showed that a high implusivity group, compared with a low implusivity group, had higher scores on suicide ideation scores and more lifetime suicide attempts. High impulsivity is particularly linked to schizophrenia patients who have clinical histories involving both suicide attempts and non-suicidal self-harming acts (Mork et al., 2013). In our recent study, we identified impulsivity as one of five significant factors that differentiated schizophrenia patients with self-harm from those without (Pluck et al., 2013).

Although the prefrontal cortex has been implicated in self-harm in depression, the neural basis of mental processes associated with suicide risk in patients with schizophrenia is not well studied. Neuroimaging studies have revealed reduced glucose metabolism in the prefrontal cortex in depressive patients with high-lethality suicide attempts compared to those with low-lethality attempts (Oquendo et al., 2003). Depression patients who completed suicide, compared with non-suicidal depression patients, had significantly higher regional cerebral blood flow (rCBF) in the right hemisphere (Amen et al., 2009). Consistent with this, Hunter and colleagues reported increased right prefrontal EEG coherence when patients with depression experienced worsening of suicidal ideation and mood symptoms during anti-depressant treatment (Hunter et al., 2010). Further, in patients with depression, high levels of mental pain associated with suicide were related to increased rCBF in the right dorsolateral prefrontal cortex (van Heeringen et al., 2010). These activations are generally consistent with observations that schizophrenia patients who attempt suicide have better prefrontal

Abbreviations: fMRI, functional magnetic resonance imaging; SH, suicide history; HC, healthy controls; DLPFC, dorsolateral prefrontal cortex; PCC, posterior cingulate cortex.

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neurocognitive functions than those that do not (Nangle et al., 2006). An exception to this is that they also display higher levels of impulsivity (Pluck et al., 2013), a feature linked to right, particularly inferior, prefrontal cortex function (Aron et al., 2014).

One of the main neuropsychological measures of response inhibition and impulsivity is the go/no-go procedure. In this task participants are asked to press a button when they see letters flashed onto a screen. Responses to these letters become pre-potent for the go trials. However they are asked to inhibit this response and to avoid pressing the button for a particular letter (the no-go trials). Impulsivity is manifest as an inability to withhold the button press for the 'no go' letter. In a functional MRI go/no-go study using a healthy sample, Horn and colleagues found a positive association between scores on Eysenck's impulsivity scale and right ventrolateral prefrontal cortex activation (Brodmann's area 44/45) (Horn et al., 2003). Kaladjian and colleagues found a positive correlation between scores on the Barratt Impulsiveness Scale and brain activation in the right ventrolateral prefrontal cortex (BA 44/45/47) in patients with schizophrenia (Kaladjian et al., 2011). However to date, no studies have examined neural activity in self-harm schizophrenia patients during performance of the go/no-go task.

The aim of the current study was to investigate the neurophysiological substrate of go/no-go response inhibition associated with self-harm in people with schizophrenia. We hypothesized that: 1) patients with schizophrenia, when compared with controls, would show less prefrontal activity during task performance, and 2) patients with a history of self-harm would show greater prefrontal activation than those without a history of self-harm. We were particularly interested in investigating whether brain activations in 'self-harm specific' areas were correlated with clinical scales for self-harm and suicide in patients with history of self-harm. By including a sample of healthy controls, we hoped to differentiate self-harm specific brain areas from schizophrenia specific brain areas during the same task.

2. Methods

2.1. Participants

Fourteen schizophrenia patients with history of self-harm, fourteen patients without history of self-harm, and 17 healthy controls participated. A standard definition was used to allocate patients to either the self-harm or no self-harm group, based on any past self-initiated acts (such as self-cutting, poisoning or jumping from a height) intended to cause self-harm (Hawton et al., 2002). The information for the classification was acquired during a clinical interview and case notes review using standard measures to record details of the acts (Gratz, 2001; Swann et al., 2005). Demographic and clinical variables for each group and any between-group differences are listed in Table 1. After fully describing the study to the participants, written informed consent was obtained. The study had Research Ethics Committee approval.

2.2. Clinical and cognitive assessments

During a clinical interview with a psychiatrist, the frequency of acts of self-harm was recorded using the Deliberate Self-Harm Inventory (DSHI), a schedule that records instances of a range of common self-harm behaviors (Gratz, 2001). Other psychological features were measured with the Barratt Impulsiveness Scale-11 (BIS-11) (Patton et al., 1995), and the Beck Hopelessness Scale (BHS) (Beck and Steer, 1993). Patients were assessed with the InterSePT Scale for Suicidal Thinking (ISST), a 12-item instrument for the assessment of current suicidal ideation in patients with schizophrenia and schizoaffective disorders (Lindenmayer et al., 2003), the Calgary Depression Scale (Addington et al., 1990); the Schedule for the Assessment of Insight (David, 1990), and social functioning was assessed with the Life Skills Profile (Rosen et al., 1989). Finally, schizophrenia symptoms were rated using the Schedules for the Assessment of Positive and Negative Symptoms (Andreasen, 1983, 1984).

All participants were also interviewed by a neuropsychologist. Premorbid IQ was estimated with the National Adult Reading Test (Corrigan and Nelson, 1998), and current IQ with the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). Sustained attention was measured using a computerized continuous performance test (CPT) (Birkett et al., 2007), and frontal executive function with the Trail Making Test (Reitan, 1958).

2.3. fMRI task, data acquisition and analysis

In an event-related fMRI design, all participants completed two functional MR runs (each run lasting 840 s, acquiring data at 420 time-points), incorporating 71 go trials, 71 no-go trials and 68 resting trials in an equi-probable go and no-go task. Each trial consisted of an event of 8 s: the presentation of each trial started with a descending series of numbers to build-up preparedness to respond ("5" for 250 ms followed by 750 ms blank screen, "4" for 250 ms followed by 750 ms blank screen…). Then, either a 'go' signal "X" or a 'no-go' signal "A" was presented for 250 ms followed by an additional 2750 ms black screen

Table 1
Demographic and clinical data.

Variable	1. Patients with SH (n = 14)	2. Patients without SH (n = 14)	3. Controls (n = 17)	Between group comparisons
Sex (No. M/F)	12/2	11/3	14/3	NS
Age (years)	43.6 ± 11.3	38.9 ± 7.3	37.9 ± 12.9	NS
Premorbid IQ (NART) [a]	103.4 ± 11.6	102.5 ± 10.0	111.6 ± 7.9	3 > 1, p = .03; 3 > 2, p = .02
Current IQ (WASI)	89.50 ± 15.936	89.79 ± 17.197	107.47 ± 18.517	3 > 1, p = .005; 3 > 2, p = .005
WASI verbal IQ	88.86 ± 21.328	90.14 ± 17.386	105.53 ± 18.822	3 > 1, p = .021; 3 > 2, p = .032
WASI performance IQ	92.14 ± 15.372	91.50 ± 15.250	107.47 ± 13.375	3 > 1, p = .006; 3 > 2, p = .004
SANS total	8.7 ± 4.6	7.7 ± 4.9		NS
SAPS total	5.8 ± 3.2	4.4 ± 3.1		NS
CPZ equivalent dose (mg/day)	466 ± 363	450 ± 288		NS
Deliberate self-harm (DSHI)	2.2 ± 2.0	0	0.29 ± .01	1 > 2, p < .001; 1 > 3, p < .001
Suicidal ideation (ISST)	3.1 ± 4.9	0.3 ± 0.8		1 > 2, p = .06
Impulsivity (BIS)	72.1 ± 6.8	68.9 ± 11.9	67.0 ± 9.2	NS
Depression (CDRS)	5.1 ± 4.2	4.2 ± 2.0		NS
Hopelessness (BHI)	9.0 ± 7.4	3.7 ± 1.9	3.0 ± 2.9	1 > 2, p = .004; 1 > 3, p = .001
Social functioning (LSP)	64.6 ± 12.7	61.4 ± 15.9		NS
Illness insight (SAI)	12.4 ± 4.2	13.4 ± 3.2		NS
Substance abuse (DSM-IV: Yes/no)	4/10	2/12	0/17	X^2 = 5.4, p = .06

Abbreviations: WASI, Wechsler Abbreviated Scale of Intelligence; CPZ, Chlorpromazine; SANS, Schedule for the Assessment of Negative Symptoms; SAPS, Schedule for the Assessment of Positive Symptoms; SAI, Schedule of Assessment of Insight; LSP, Life Skills Profile.

[a] Estimated from scores on the National Adult Reading Test (NART).