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.

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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

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).

for responding. This equi-probable go/no-go task enables the number of 'go' and 'no-go' trials to be constant, so that brain activity associated with novelty (rare target events) can be controlled for (Liddle et al., 2001). Trial order was optimized for statistical power and psychological validity using a genetic algorithm (Wager and Nichols, 2003). All participants had a practice session immediately before fMRI.

Functional imaging datasets were acquired using a 3T scanner (Achieva 3.0T, Philips Healthcare, Best, The Netherlands) at the University of Sheffield. A single-shot, gradient recalled, echo-planar technique was used to acquire 22 × 6mm thick contiguous transverse slices at 420 time points per run (TR = 2000 ms, TE = 35 ms, SENSE factor = 1.5, in-plane resolution 1.8 × 1.8 mm). A high resolution T_1-weighted structural MRI was also acquired for each participant using a 3D MPRAGE sequence (TR = 15 ms; TE = 4.4 ms; 0.8 × 0.8 × 0.8 mm voxel size). Data were analyzed using statistical parametric mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm). Pre-processing involved re-alignment, unwarping, co-registration of the mean functional image with the structural scan of each participant, spatial normalization, and spatial smoothing using a Gaussian kernel of full-width half-maximum 6 mm.

In the first level of analysis for individual participants, we used only correct no-go and go trials, to create statistical parametric maps for no-go minus rest, go minus rest, no-go minus go and go minus no-go trials. For the second-level group statistics, within-group t-tests were performed using the random-effects approach with a significance threshold of p < .05, corrected for family-wise error-rate, with a cluster extent threshold of 5 voxels. We further performed a whole-brain analysis of variance (ANOVA) for all three groups. Significant clusters associated with the main effect of group were identified using a height threshold of p < .001 (uncorrected for multiple comparisons) and a cluster extent threshold of 5 voxels. Anatomical localizations were transformed into the stereotactic space of Talairach and Tournoux. The mean activation in each of the clusters for each participant was extracted using the MarsBaR toolbox (http://marsbar.sourceforge.net/). These data were then used to conduct between-group and correlation analyses using SPSS (Version 17, SPSS Inc, Chicago).

All correlation analyses of brain activation with task performance, clinical and cognitive measures were conducted with a threshold of p = .0083 (i.e., .05 divided 6, the number of regions of interest, see Section 3) and accordingly, adjusted p-values are reported hereafter. All correlation analyses were initially conducted in each group separately, in order to avoid the possibility that group differences might have an impact on the correlations. The same correlation analyses were then later conducted with all participants.

3. Results

3.1. Behavioral performance during fMRI

Behavioral data during scanning showed that all groups performed with comparable high accuracy (self-harm patient group: 94.6%, SD = 7.4; non-self-harm patient group: 96.1%, SD = 4.4; control group: 97.2%, SD = 4.6). There were no significant between-group differences in the number of total correct responses, commission or omission errors. Likewise, the mean reaction time (RT) for go trials was not significantly different across groups (self-harm patient group: 433.6 ms, SD = 110.9; non self-harm patient group: 399.8, SD = 105.2; control group: 355.8 ms, SD = 93.8) [$F_{(2, 42)}$ = 2.23; p = .12]. However, RT variability was significantly different between groups [$F_{(2, 42)}$ = 3.76; p < .05], with the self-harm patient group exhibiting a significant increase of RT variability compared with the control group in a post-hoc pairwise comparison (p < .01).

3.2. fMRI findings

As shown in Table 2, the no-go versus rest contrast showed anterior cingulate cortex activation across all groups. The control group activated

Table 2
Brain areas significantly activated during correct no-go versus rest trials in control group and patient groups.

Region (BA)	Coordinate (x, y, z)			Cluster size	Z-value
Healthy controls					
Left ACC (32)	−6	14	38	625	6.44
Right ventrolateral prefrontal cortex (VLPFC) (47)	32	25	1	341	6.08
Left insular	−36	10	−2	177	6.07
Right posterior cingulate (23)	6	−22	23	222	6.06
Right cerebellum	2	−63	−22	154	5.33
Left precentral gyrus (6)	−46	−2	41	13	5.13
Right inferior parietal lobule (40)	30	−45	37	11	5.03
Right thalamus	8	−17	16	5	4.79
Left thalamus	−14	−10	0	7	4.76
Patients with history of self-harm					
Left ACC (32)	−4	12	40	33	5.49
Right precuneus (7)	30	−47	39	24	5.26
Right medial frontal cortex (32)	10	12	47	86	5.18
Left fusiform gyrus (37)	−42	−63	−9	23	5.04
Right ACC (32)	8	21	30	8	4.75
Patients without history of self-harm					
Right superior parietal lobule (7)	30	−49	39	168	6.61
Left precentral gyrus (6)	−40	2	35	119	5.97
Left fusiform gyrus (19)	−40	−65	−9	70	5.71
Right cerebellum	8	−71	−18	69	5.48
Right ACC (32)	8	18	41	175	5.45
Left precuneus (7)	−26	−59	34	146	5.36
Left cerebellum	−32	−52	−21	32	5.27
Left cerebellum	−34	12	1	9	4.93
Left inferior parietal lobule (40)	−40	−45	37	15	4.76
Right superior frontal gyrus (6)	8	8	53	7	4.74

right ventrolateral prefrontal cortex (VLPFC, BA 47), which was absent in the patient groups. Conversely, precuneus/posterior cingulate activation (BA 7) was seen in the patient groups, but not in the control group. The no-go versus go contrast did not show any significant brain areas in any groups. The go versus rest contrast in all participant groups showed activations in left motor and sensory cortices, anterior cingulate/medial prefrontal cortex, and right cerebellum (Supplementary Table 1). In the go versus no-go contrast, control participants activated left pre and postcentral gyri, and right cerebellum (lobule V). For the same contrast in patient groups, motor and sensory cortical areas, and the cerebellum were activated as in the control group, with the additional recruitment of the basal ganglia and insula (Supplementary Table 2).

A three-group ANOVA for the no-go versus rest contrast showed a significant main effect of group in the right VLPFC (BA 47) [$F_{(2, 42)}$ = 11.12; p < .001], the right DLPFC (BA 9) [$F_{(2, 42)}$ = 10.89; p < .001], the ventral anterior cingulate cortex (ventral ACC; BA 24) [$F_{(2, 42)}$ = 10.76; p < .001], the PCC (two foci: BA 23, $F_{(2, 42)}$ = 9.08; p < .01, and BA 31, $F_{(2, 42)}$ = 11.10; p < .001,) and the thalamus [$F_{(2, 42)}$ = 10.67; p < .001]. Between-group pairwise comparisons revealed three distinct patterns (see Table 3). First, compared with the two patient groups, the control group showed increased activation in the right VLPFC (BA 47), ventral ACC (BA 24) and right thalamus: no difference was found between the two patient groups. Second, in the right dorsal PCC (BA 31), the control group showed significantly less activation, compared with the patient groups. Hence the above two networks were sensitive to diagnosis (i.e., schizophrenia versus control). Finally, activations in the right DLPFC (BA 9) and the left PCC (BA 23) differentiated all three groups (activation in the control group > self-harm patient group > non self-harm patient group; See Table 3). Hence, activities in these areas were sensitive to self-harm as well as the diagnosis of schizophrenia.

In terms of task performance (corrected threshold of p = 0.0083), activity in the ventral ACC (BA 24) was significantly negatively correlated with the number of omission errors during scanning (r = −.584, p = .046) in the self-harm patient group. The same correlation was significant when all participants were combined (r = −.419, p = .024).

Table 3
Significant regions exhibiting the main effect of group in the analysis of variance (1 = Patients with SH, 2 = Patients without SH, 3 = healthy control participants).

Region (BA)	Coordinate (x, y, z)	Cluster size	Z value	Between group comparisons
Right ventrolateral prefrontal cortex (VLPFC) (47)	28, 30, −14	34	3.99	3 > 1, p < .001; 3 > 2, p < .001
Left ventral anterior cingulate (24)	−14, 11, 31	14	3.88	3 > 1, p < .001; 3 > 2, p < .001
Right dorsal posterior cingulate (31)	6, −52, 47	8	3.73	1 > 3, p < .001; 2 > 3, p < .001
Right dorsolateral prefrontal cortex (9)	16, 42, 31	17	3.67	3 > 1, p = .021; 3 > 2, p < .001; 1 > 2, p = .037
Right thalamus	8, −19, 16	5	3.38	3 > 1, p < .001; 3 > 2, p < .01
Left ventral posterior cingulate (23)	2, −20, 27	8	3.21	3 > 1, p = .038; 3 > 2, p < .001; 1 > 2, p = .05

In addition, activity in both the same ventral ACC and thalamus was negatively correlated with RT variability in all participants (r = −.541, p = .0007 and r = −.477, p = .006).

3.3. Association with clinical and cognitive measures

In the control participants, activity in the right DLPFC (BA 9) was positively correlated with BHS scores (r = .688, p = 0.014, Fig. 1C). No other correlations with the BHS were statistically significant. In addition, for all participants combined, activity in the thalamus was negatively correlated with DSHI (r = −.390, p = 0.048) and with BHS scores at a trend level (r = −.386, p = .052).

In the self-harm patient group, activity in the right DLPFC (BA 9) was positively correlated with ISST scores (r = .715, p = .024, see Fig. 1D) and activity in the left PCC (BA 23) was negatively correlated with CDSS scores (r = −.687, p = .039). However, these associations were not found to be significant in the non-self-harm patient group. Finally,

the severity of positive and negative symptoms was not associated with any brain activations found during scanning.

Correlations were performed between activity in the regions of interest and neuropsychological data. Right dorsal PCC (BA 31) activity and verbal IQ scores were negatively correlated at a trend level in the control group (r = −.573, p = .09). Accordingly, the direction of association between BA 31 activity and cognitive performance was negative for all tests across groups. This is in line with the current findings showing that control participants exhibited decreased activation in this area compared with the patient groups. Finally, in all participants, right VLPFC activity (BA 47) was negatively correlated with Trails A (r = −.407, p = .033) and B (r = −398, p = .041), indicating that increased activity in this area was associated with better performance. The right dorsal PCC (BA 31) activity was negatively associated with IQ scores (significant for full IQ, r = −539, p < .001, as well as verbal, r = −.546, p < .001 and performance scores, r = −.403, p < .05). On the other hand, CPT performance (d') was positively correlated with
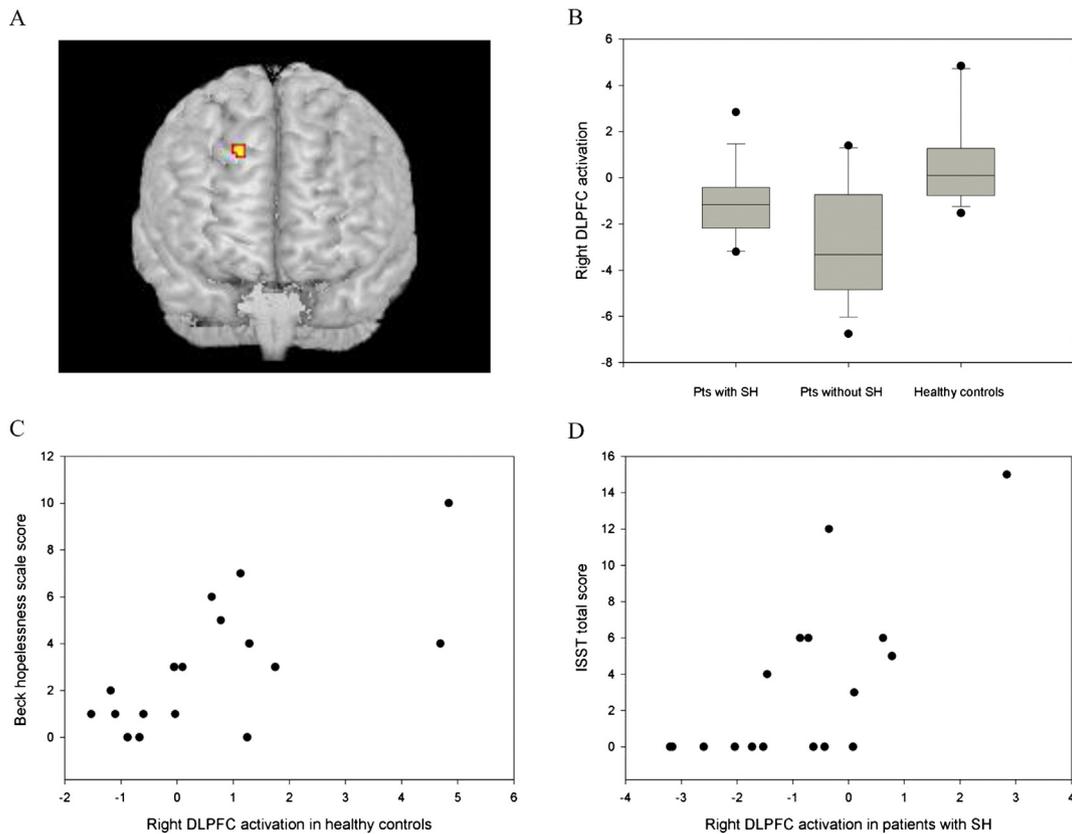
Fig. 1. Right dorsolateral prefrontal cortex (BA 9; 16, 42, 31) shown in the main effect of group from a three-group ANOVA for the no-go versus rest contrast (A) and box-plot displaying central tendency and variability for the right DLPFC activation for the three groups (B). Right DLPFC activity was positively correlated with Beck hopelessness scale scores (BHS) in healthy controls (C) and with the severity of suicidal thinking in patients with history of self-harm (ISST total scores, D). Note that this right DLPFC activity associated with hopelessness and suicidal thinking appears to be task independent, because activity in the same area in the go-rest contrast showed a similar level of significant association with total BHS scores in healthy controls (r = .629, p = .049) and with ISST total scores in patients with history of self-harm (r = .689, p = .036).

activations in the ventral ACC (BA 24, r = .420, p = .025) and thalamus (r = .401, p = .038).

4. Discussion

The primary finding is that activations associated with response inhibition using the go/no-go paradigm varied between the groups, indicating brain regions associated with self-harm in people with schizophrenia. Activations in the right DLPFC and left ventral PCC were higher in the control group than in those schizophrenia patients with self-harm histories, which in turn were higher than in patients without histories of self-harm. This suggests that activity in these areas is important in the phenomenon of self-harm by schizophrenia patients. Further support for this is provided by two statistical observations. First, for the patients who had self-harmed, go/no-go related activity in the right DLPFC was significantly correlated with severity of suicidal ideation. Second, hopelessness (a significant predictor of self-harm) was positively correlated with right DLPFC activity. These findings suggest a role for the right DLPFC in suicide and other self-harm behaviors.

The right DLPFC (BA 9) has previously been identified as a brain area showing alterations in function both at rest and during cognitive task performance in patients with major depression (Fitzgerald et al., 2006). In addition, studies have demonstrated antidepressant effects of inhibitory transcranial magnetic stimulation to the right DLPFC (Klein et al., 1999). Furthermore, relatively increased rCBF in right BA 9 in depressed patients experiencing high levels of mental pain associated with suicidality has been reported (van Heeringen et al., 2010). Although BA 9 is a relatively long and large area, the peak coordinates of right BA 9 in van Heeringen et al.'s study (13, 39, 30) were in close proximity to ours (16, 42, 31). Thus, brain imaging findings from depression and our findings converge on a role for BA 9 in self-harm. This has significant implications for future neuromodulation studies targeting suicidal thinking and self-harm behaviors in these clinical groups. It should also be noted that this right DLPFC activity associated with suicidal thinking and hopelessness appears to be task independent, as this same area's activity in the go-rest contrast showed a similar level of significant associations (See Fig. 1 Legend). Perhaps, though maladaptive, maintaining suicidal thinking requires working memory functions of the DLPFC.

In addition to the right DLPFC activations, we also found that ventral posterior cingulate activation (BA 23) differentiated all three groups whereas dorsal posterior cingulate activation (BA 31) differentiated schizophrenia groups from controls. Furthermore, lower activity in the ventral PCC was associated with depression in the schizophrenia patients with self-harm. On the other hand, dorsal PCC activity was mainly related to cognitive performance; such that decreased activity in this area was associated with better cognitive performance. These findings are consistent with emerging evidence of anatomical and functional differences between the ventral and dorsal posterior cingulate. Leech and colleagues have suggested that the ventral PCC is more involved in internally directed attention and emotion along with its functional connectivity with the temporal lobes, whereas the dorsal PCC is actively involved in the control/switch of internally and externally focused attention and cognition in conjunction with the medial prefrontal cortex (Leech et al., 2011).

A further finding is that the schizophrenia patients, in comparison to the controls, consistently failed to activate the right VLPFC, left ventral ACC, and right thalamus. Hence, these are sensitive to schizophrenia diagnosis during scanning using the go/no-go task. Our findings are consistent with previous schizophrenia studies that have used the same equi-probable go/no-go task reporting decreased right VLPFC activity (Kaladjian et al., 2007). While a more recent study by the same group found a positive correlation between scores on Barratt's trait impulsiveness scale and activities in the right VLPFC in patients with schizophrenia during a go/no-go task (Kaladjian et al., 2011), we did not find such an association. This inconsistency may be attributable to low

impulsivity scores in our patient groups, as the healthy control group's impulsivity scores were not statistically different.

Considerable evidence suggests that ACC-thalamic system activity is associated with increased alertness and concentration (Paus, 2001). Compared with the control group, the schizophrenia patients exhibited decreased activation in the ventral ACC and thalamus. Previous studies utilizing various response inhibition tasks have also found that ACC and thalamic activation were reduced in patients with schizophrenia (Barkataki et al. 2008; Rubia et al., 2001). Furthermore, we found that ventral ACC activity was significantly negatively correlated with the number of omission errors and response variability during scanning and positively correlated with CPT performance. This suggests that alertness and concentration may be mediated by the activity in the ACC-thalamic system during the go/no-go task, and patients with schizophrenia fail to utilize this system during performance.

However, it should be noted that overall task performance did not vary between the groups, despite numerous differences in neural processing revealed by fMRI. Such observations are common in functional imaging studies of psychiatric patients. In some cases, behavioral performance is worse despite normal brain activations. For example, a recent study using the go/no-go task with bipolar I patients found that despite poor task performance compared to controls, imaging data did not reveal any differences (Welander-Vatn et al., 2013). In other studies, such as ours, activations are abnormal despite normal behavioral performance (Eyler et al., 2004). These differences probably reflect abnormalities of neural processing by psychiatric patients that can manifest as either alterations to functional routes in the brain or less efficient processing. In the case of the current research, it is suggested that the task was performed by the schizophrenia patients with less reliance on the DLPFC, VLPFC and thalamus of the right hemisphere and cingulate regions of the left hemisphere, with compensatory strategies involving the right dorsal PCC (BA 31), which was found to be more active in the patients compared to the controls in the no-go versus rest contrast.

In addition to the neural activation findings, we observed that patients with a history of self-harm showed significantly higher levels of hopelessness when compared to those without a history of self-harm. Hopelessness has been linked to suicide among people with schizophrenia (Steblaj et al., 1999). However, we noted previously with a larger sample (Pluck et al., 2013), that neither severities of positive nor negative symptoms were linked to self-harm. A recent study of 509 schizophrenia patients has also reported that positive and negative symptoms are not predictive of suicide attempts (Jovanovic et al., 2013). Similarly, severity of positive and negative symptoms was not associated with any self-harm related brain activations in our study. These findings suggest that we should look beyond the core symptoms to improve prevention strategies for self-harm in patients with schizophrenia. This could include measures of impulsiveness or hopelessness, as well as the possibility of functional imaging to identify those patients at risk.

There are some limitations to this study. First, our no-go versus go contrast did not show any significantly activated brain areas in any group. This was partly because 'go' trials also activated inhibition-related brain areas including bilateral VLPFC, in addition to motor and sensory areas. This finding could indicate that response selection (in 'go' trials) and response inhibition (selecting not to respond in no-go trials) share the same neural circuitry (Mostofsky and Simmonds, 2008). Furthermore, the use of a simple, relatively non-demanding, go/no-go task in our study may have contributed to the non-significant finding, as cognitive demands for no-go trials would be lower compared with a working memory go/no-go task (Simmonds et al., 2008). Nevertheless, the no-go versus rest contrast was sufficient for the purpose of comparing patients with a history of self-harm to those without a history of self-harm and to healthy controls.

Second, an intriguing finding in this study was that although right DLPFC activation was not significant in the no-go versus rest contrast in any group, it was significantly different across groups from the

ANOVA. This observation suggests that right DLPFC activity in our study may be task-independent, despite significant right DLPFC activations during response inhibition having commonly been reported (Nakata et al., 2008). Indeed, we isolated activity in the same coordinates in the go versus rest contrast, and confirmed that we found significant correlations as in the no-go versus rest contrast. In order to test this idea further, studies should employ separate paradigms to confirm whether right DLPFC activity differences exist between patients with- and without the tendency to self-harm. Finally, our sample size was relatively small. Hence, other group differences may not have been detected between patients with and without self-harm. For example, in a larger sample we previously found that patients with history of self-harm had higher impulsivity scores than patients without history of self-harm (Pluck et al., 2013). In the present study, however we did not find such a difference.

5. Conclusion

In conclusion, patients with schizophrenia who have a history of self-harm were distinguishable from those without a history of self-harm and control participants by their neural activity in the right DLPFC and left ventral PCC. Furthermore, right DLPFC activation is significantly positively associated with suicidal thinking in patients with a history of self-harm. This area could be a target for future neuromodulation studies to treat suicidal thinking in patients with schizophrenia. This work is the first step towards an attempt to help predict self-harm and suicide in patients with schizophrenia by their neural responses.

The conflict of interest

None.

Acknowledgment

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.pnpbp.2015.03.005.

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