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Effects of childhood trauma on left inferior frontal gyrus function during response inhibition across psychotic disorders

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Original Article

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Abstract

Background. Childhood trauma is a risk factor for psychosis. Deficits in response inhibition are common to psychosis and trauma-exposed populations, and associated brain functions may be affected by trauma exposure in psychotic disorders. We aimed to identify the influence of trauma-exposure on brain activation and functional connectivity during a response inhibition task.

Methods. We used functional magnetic resonance imaging to examine brain function within regions-of-interest [left and right inferior frontal gyrus (IFG), right dorsolateral prefrontal cortex, right supplementary motor area, right inferior parietal lobule and dorsal anterior cingulate cortex], during the performance of a Go/No-Go Flanker task, in 112 clinical cases with psychotic disorders and 53 healthy controls (HCs). Among the participants, 71 clinical cases and 21 HCs reported significant levels of childhood trauma exposure, while 41 clinical cases and 32 HCs did not.

Results. In the absence of effects on response inhibition performance, childhood trauma exposure was associated with increased activation in the left IFG, and increased connectivity between the left IFG seed region and the cerebellum and calcarine sulcus, in both cases and healthy individuals. There was no main effect of psychosis, and no trauma-by-psychosis interaction for any other region-of-interest. Within the clinical sample, the effects of trauma-exposure on the left IFG activation were mediated by symptom severity.

Conclusions. Trauma-related increases in activation of the left IFG were not associated with performance differences, or dependent on clinical diagnostic status; increased IFG functionality may represent a compensatory (overactivation) mechanism required to exert adequate inhibitory control of the motor response.

Introduction

Traumatic life events are risk factors for psychosis (Varese *et al.* 2012; Green *et al.* 2014; Read *et al.* 2014; Gibson *et al.* 2016) and are associated with morphological and functional alterations in brain regions critical for executive functioning (Hart & Rubia, 2012; Teicher & Samson, 2013; Lim *et al.* 2014; Teicher *et al.* 2016). Executive functions represent candidate cognitive endophenotypes that cut across diagnostic categories (Reichenberg *et al.* 2009; Hill *et al.* 2013) with deficits in response inhibition, in particular, being proposed to underlie core symptoms of schizophrenia and related psychoses (Peters *et al.* 2000; Ivleva *et al.* 2012). Cognitive functions in psychotic disorders are influenced by childhood trauma exposure (Lysaker *et al.* 2001; Aas *et al.* 2011; Shannon *et al.* 2011), but the associated brain mechanisms are yet to be determined. Here, we investigated the effects of trauma exposure on functional brain indices of response inhibition in patients with schizophrenia or schizoaffective disorder (together referred to as SZ) or psychotic bipolar-I disorder (BD), relative to trauma-exposed and non-exposed healthy individuals.

Several studies now report trauma-related structural brain aberration in mixed samples of psychotic disorders (i.e. comprising schizophrenia, schizoaffective disorder, and psychotic bipolar cases), including reduced grey matter in the left dorsolateral prefrontal cortex (DLPFC) and the anterior cingulate cortex (ACC) (Sheffield *et al.* 2013), or in the right DLPFC in a sample of schizophrenia patients only (Cancel *et al.* 2015). However, relatively few studies have examined the effects of childhood trauma on cognitive brain *function* in cross-disorder groups of psychosis patients. One functional brain imaging study of a mixed psychosis sample has shown trauma-related inefficient recruitment of the inferior parietal lobule (IPL) during working memory performance (Quidé *et al.* 2017). While this study was the first to show trauma-related dysfunction in this inhibitory brain region (IPL), adequate

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response inhibition also critically involves the supplementary motor area (SMA) and the inferior frontal gyrus (IFG), in addition to the functional integrity of the DLPFC and dorsal ACC (dACC) (Aron, 2011; Criaud & Boulinguez, 2013). Abnormal functionality of these regions has been demonstrated in previous studies without reference to trauma exposure. For example, schizophrenia patients have shown decreased activation in the dACC, right IFG and caudate, and increased connectivity between the dACC and bilateral DLPFC, IFG and IPL compared with healthy participants during an inhibitory (Go/No-Go Flanker) task (Sambataro *et al.* 2013). Similarly, decreased IFG activation has been associated with fearful face inhibition (using a face-emotion Go/No-Go task) in youths at high risk for BD (Roberts *et al.* 2013), while dACC function appears to be intact in adult BD cases (Welander-Vatn *et al.* 2013).

In non-psychotic young people, trauma exposure is consistently associated with increased activation in the dACC during inhibition. Youth exposed to stress (some with posttraumatic stress symptoms) also show increased activation in the medial prefrontal cortex (mPFC), the IFG, pre-postcentral gyri, striatum and posterior insula, as well as decreased activation of the DLPFC during (competent) inhibition (Carrion *et al.* 2008; Mueller *et al.* 2010). Interestingly, trauma-exposed young people with psychiatric comorbidities, including phobia, mood, anxiety, conduct and posttraumatic stress disorders (PTSD) show increased activation in the dACC, SMA and dorsomedial PFC in the context of deficient inhibitory performance (Lim *et al.* 2015). Overall, these findings indicate functional alterations in key brain regions (dACC, IFG, IPL, SMA and DLPFC) for response inhibition that have been independently associated with psychosis and childhood trauma exposure, but to date have not been investigated together.

Given the high prevalence of childhood trauma exposure reported in psychotic disorders (Duhig *et al.* 2015), it is possible that exposure to childhood trauma impacts brain maturation, and contributes to the development of psychosis-related brain alterations, via a traumatogenic pathway to psychosis (Read *et al.* 2014). Alternatively, symptoms of disorder may precede the development of brain abnormalities in psychosis and mood disorders arising in the context of trauma exposure. While we did not have access to a developmental sample here, we set out to examine brain activation and functional connectivity associated with childhood trauma exposure during a Go/No-Go Flanker task (Blasi *et al.* 2006; Sambataro *et al.* 2013), in a mixed diagnostic group of patients with schizophrenia, schizoaffective disorder and psychotic BD, relative to non-exposed clinical cases, and both trauma-exposed and non-exposed healthy individuals. Given greater symptom severity associated with childhood trauma exposure (Alvarez *et al.* 2011; Duhig *et al.* 2015), we explored associations between trauma, brain function and symptom severity, including formal tests of the potential mediation of the effects of trauma exposure on brain function by symptom severity, or whether brain function was a significant mediator of the effects of trauma exposure on symptom severity. We specifically hypothesized that trauma-exposure would be associated with *increased* activation of regions specifically involved in the performance of complex response inhibition (left and right IFG, right DLPFC, right IPL and right SMA; Criaud & Boulinguez, 2013), and the dACC, regardless of diagnostic status. In addition, we expected to observe trauma-related alterations in the functional connectivity between regions specific to inhibition (IFG, SMA) and common cortical regions involved in executive functions (IPL, DLPFC). Given that previous studies have found psychosis-related abnormalities in these brain regions, regardless of trauma-exposure, we also expected to observe main effects of psychosis and trauma in overlapping regions such as the dACC, though differentiated in the direction of activation. That is, we expected decreased activation of the dACC in association with a diagnosis of schizophrenia, schizoaffective disorder or bipolar disorder (reflecting typical regional activation in psychosis patients) relative to healthy controls (HCs), while there would be increased dACC activation in trauma-exposed participants (cases and controls) relative to non-exposed individuals, on the basis of previous findings in ostensibly healthy individuals (Hart & Rubia, 2012; Teicher & Samson, 2013; Teicher *et al.* 2016). With regard to the tests of mediation, we expected that symptom severity would at least partially mediate the relationship between trauma exposure and inhibitory brain activation, in the mixed psychosis sample.

Methods

All participants were volunteers who provided informed consent according to procedures approved by the UNSW Human Research Ethics committees (HC12384), the South East Sydney and Illawarra Area Health Service (HREC 09/081) and St Vincent's Hospital (HREC/10/SVH/9).

Participants

Participants included 112 clinical cases meeting ICD-10 criteria (WHO, 2008) for lifetime diagnoses of schizophrenia ($n = 36$), schizoaffective disorder ($n = 20$) or BD with psychosis ($n = 56$). Diagnoses were confirmed using the OPCRIT algorithm (McGuffin & Farmer, 1991) applied to interviewer ratings on the Diagnostic Interview for Psychosis (Castle *et al.* 2006). There were 53 HCs with no personal history of DSM-IV Axis-I disorder and no history of psychotic disorders in their first-degree biological relatives on the basis of the Mini-International Neuropsychiatric Interview (Sheehan *et al.* 1998). Participants were recruited from local community health services, the Australian Schizophrenia Research Bank (ASRB; Loughland *et al.* 2010), the Black Dog Institute Bipolar Disorders clinic (Mitchell *et al.* 2009), and via local community advertisements. All included participants were aged between 18 and 65 years old, were eligible for magnetic resonance imaging protocols and did not meet the following exclusion criteria: inability to communicate sufficiently in English, current neurological disorder, lifetime head injury with loss of consciousness, substance abuse or dependence in the past 6 months, and having received electroconvulsive therapy within the past 6 months.

Materials

Clinical and cognitive assessments

Current symptom severity was determined using the Depression, Anxiety and Stress Scale (DASS; Lovibond & Lovibond, 1995), the Positive and Negative Syndrome Scale (PANSS; Kay *et al.* 1989), the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979), the Bipolar Depression Rating Scale (BDRS; Berk *et al.* 2007) and the Young Mania Rating Scale (YMRS; Young *et al.* 1978). Participants also completed the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) as an index of current IQ, and handedness was determined using the Edinburgh Handedness Inventory

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(Oldfield, 1971). Medication dosages were measured in imipramine (IMI) equivalents for antidepressants and chlorpromazine equivalents (CPZ) for antipsychotic drugs (Leucht *et al.* 2003; Woods, 2003); the number of cases using mood stabilizers (including lithium, carbamazepine, valproate and lamotrigine) was recorded in lieu of dosage equivalents for these drugs.

Childhood trauma exposure

Exposure to childhood trauma was measured using the short form (25 items) of the Childhood Trauma Questionnaire (CTQ; Bernstein *et al.* 2003). The CTQ is a self-report questionnaire that retrospectively measures domains of emotional (EA), physical (PA) and sexual (SA) abuse, as well as physical (PN) and emotional (EN) neglect. For each domain, a score is calculated from five items rated on a five-point Likert scale ranging from 1 (never true) to 5 (very often true). Participants were allocated to trauma-exposed groups if they endorsed moderate to extreme levels of trauma on at least one CTQ subscale (i.e. EA > 12; PA > 9; SA > 7; EN > 14; PN > 9) (Bernstein *et al.* 2003; Shannon *et al.* 2011; Mørkved *et al.* 2017; Quidé *et al.* 2017). Non-exposed participants were defined as those not reporting moderate to extreme levels of trauma on any CTQ subscale. According to these criteria, there were 71 exposed clinical cases (20 schizophrenia, 14 schizoaffective and 37 bipolar cases), 41 non-exposed cases (16 schizophrenia, 6 schizoaffective and 19 bipolar cases), and 21 exposed HC relative to 32 non-exposed HC.

Functional magnetic resonance imaging (fMRI) stimuli and modified Flanker task

We measured blood-oxygenation level dependent (BOLD) signal changes during the performance of a standard Go/No-Go Flanker task (Blasi *et al.* 2006; Sambataro *et al.* 2013). In this event-related paradigm, a central arrow pointing left or right was presented on each trial, and flanked by two pairs of symbols (arrows, boxes or X's). Participants were asked to indicate the direction of the central arrow as quickly and accurately as possible. All participants completed the same pseudo-random sequence of trials, which included four experimental conditions. On 'Congruent' trials ($N = 41$) the central arrow was flanked by congruently oriented arrows, while on 'Incongruent' trials ($N = 40$) the flanking arrows pointed in the opposite direction. On 'Neutral' trials ($N = 31$) the central arrow was flanked by task-irrelevant boxes, and on 'No-Go' trials ($N = 33$), two pairs of lateral X's instructed the participant to inhibit any motor response. Each trial was presented for 800 ms and a fixation crosshair was presented between each trial (inter-trial-interval = 2200–5200 ms). Stimuli were displayed by Presentation software (Neurobehavioral Systems, Inc.) on a Philips LCD monitor at the rear of the magnet, and viewed by the participant via a standard head coil mirror. A Cedrus Lumina response box was used to record behavioural responses. Before entering the scanner, participants were allowed to practice the behavioural task to ensure comprehension.

fMRI data acquisition and pre-processing

We acquired 306 whole brain T2* weighted echo-planar images (EPI), slice thickness 4, 0.3 mm gap, 32 axial slices in ascending order, TR 2000 ms, TE 30 ms, flip angle 80°, matrix 96 × 96, field of view 240 mm, on a Philips 3 T Achieva TX scanner (Philips Healthcare, Best, The Netherlands) with a 32-channel head coil, housed at Neuroscience Research Australia (Randwick, NSW, Australia). A high-resolution T1-weighted anatomical scan (MPRAGE) was also obtained for each participant for registration and screening; TR 8.9 ms, TE 4.1 ms, field of view 240 mm, matrix 268 × 268, 200 sagittal slices, slice thickness 0.9 mm (no gap). A radiologist reviewed all scans, and all images were visually inspected to ensure that no gross abnormalities were evident. Image processing and analyses were performed using SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm) in Matlab r2011b (Mathworks Inc., Sherborn, MA, USA), and SPM12 for the estimation of cluster extent accounting for multiple comparison correction for *F*-tests. The pre-processing pipeline is described in online Supplementary Material.

Regions-of-interest (ROIs)

ROIs for functional activation and connectivity analyses were defined as 6 mm radius spheres for the left and right IFG, the right IPL, right DLPFC, right SMA and dACC. The ROIs were built using the Marsbar toolbox for SPM8 (http://marsbar.sourceforge.net; Brett *et al.* 2002) and placed around coordinates published in a meta-analysis of complex Go/No-Go tasks (Criaud & Boulinguez, 2013). Details on ROIs derivation are provided in online Supplementary Material.

Task-related functional connectivity

Whole-brain functional connectivity (functional coupling) during response inhibition with each of the separate seed regions (defined above) was estimated using the generalized Psycho-Physiological Interactions toolbox (gPPI, v7.12, https://www.nitrc.org/projects/gppi; McLaren *et al.* 2012). Details are provided in online Supplementary Material.

Analyses

Behavioural and clinical data

Descriptive statistics were performed using SPSS 23 (IBM).

Brain imaging

Main effects of trauma, diagnosis, and their potential interaction on brain function in candidate ROIs were investigated using a 2 × 2 multivariate analysis of variance (MANOVA), with *trauma* (exposed/non-exposed) and *diagnosis* (cases/controls) as fixed factors, within SPM8. Statistical significance was set at $p < 0.05$ for the multivariate level, and was appropriately adjusted for the six ROIs at the univariate level using a strict Bonferroni correction ($p < 0.008$). A series of whole-brain 2 × 2 ANOVAs were also conducted to estimate main effects of trauma, diagnosis and their interaction on *functional connectivity* with each seed region separately. Statistical significance was set with an initial voxel-level threshold of $p < 0.001$ uncorrected, to which a FWE-correction at the cluster-level was applied [$p(\text{FWEc}) < 0.05$]; an additional Bonferroni correction was applied to the cluster statistics due to the number of seed regions explored [$p(\text{FWEc}) \leqslant 0.008$].

Correlational analyses

Additional Pearson's correlations were used to explore associations between activation in each ROI separately and task performance ($p < 0.05$). Given differences in levels of antipsychotic drug use among trauma-exposed and non-exposed cases (see the 'Results' section), we investigated potential associations between brain function (ROIs) and CPZ-equivalent medication levels using Pearson's product-moment correlations ($p < 0.05$, two-tailed). Similarly, the association between symptom severity

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(PANSS positive, negative and general sub-scores) and brain function was explored ($p < 0.05$, two-tailed).

Mediation analyses

A power analysis using G*Power 3.1.9.2 (Faul *et al.* 2007; Faul *et al.* 2009) indicated that a minimum of 68 participants was necessary for these mediation analyses ($F_{2,65} = 3.14$, $\lambda = 10.20$), and thus confirmed that our clinical sample ($n = 112$) was of sufficient size to achieve 80% power for detecting a medium ($f^2 = 0.15$) effect for two predictors ($\alpha = 0.05$). Two mediation models were investigated using the PROCESS toolbox for SPSS (v2.16.1, www.afhayes.com; Hayes, 2013): (1) the potential role of left IFG activation in mediating the effects of trauma exposure on PANSS symptom severity (PANSS positive, negative and general scales, separately), and (2) the potential role of symptom severity in mediating the effects of trauma exposure on left IFG activation.

Results

Sample characteristics

Table 1 presents descriptive details for experimental groups defined by trauma exposure. One-way analyses of variance (ANOVAs) and χ^2 tests indicated that these experimental groups did not differ in age, sex or handedness. However, all cases (regardless of trauma exposure) and exposed HCs were significantly less educated than non-exposed HCs (all $p \leqslant 0.015$). Only exposed cases had lower IQ levels than non-exposed HCs ($p = 0.018$). Fischer's Exact test indicated that diagnoses were distributed equally across trauma-exposed and non-exposed clinical groups. Exposed and non-exposed cases did not differ in terms of antidepressant dosages ($p = 0.828$) or mood stabilizer use ($p = 1.000$), but exposed cases reported greater levels of antipsychotic dosages than the non-exposed cases ($p = 0.032$).

One-way ANOVAs conducted on CTQ subscales indicated that the trauma-exposed groups (cases and HCs) reported greater levels of emotional and physical abuse compared with non-exposed groups (all *post hoc* tests $p \leqslant 0.011$); only the trauma-exposed cases additionally reported greater levels of sexual abuse (all $p < 0.001$), and emotional (all $p < 0.001$) and physical neglect (all $p < 0.001$), compared with non-exposed groups. Finally, exposed cases reported greater levels of emotional abuse when compared to exposed HCs ($p = 0.029$), who in turn reported greater levels of physical neglect than non-exposed HCs ($p = 0.001$). Overall, clinical and non-clinical trauma exposed cases reported greater CTQ total score than both non-exposed groups (all $p < 0.001$), with the exposed cases reporting a larger total trauma severity score than exposed HCs ($p = 0.012$).

One-way ANOVAs on the DASS-21 indicated that all cases reported greater levels of depression (for all *post hoc* tests, $p \leqslant 0.019$), anxiety (all $p \leqslant 0.001$) and stress (all $p \leqslant 0.001$), regardless of trauma exposure, relative to the non-exposed HC group. The DASS-21 subscales for exposed cases were also significantly greater than for exposed HCs (all $p \leqslant 0.005$). Two-sample *t* tests indicated that exposed cases also reported greater psychotic symptom severity (all PANSS subscales; all $p \leqslant 0.040$) as well as depression (MADRS; $p < 0.001$), bipolar (BDRS; $p = 0.001$) and mania (YMRS; $p = 0.034$) levels than the non-exposed cases.

Among the exposed cases and controls, there were high rates of endorsing more than one type of trauma, with 59% of exposed cases and 57% of exposed HCs reporting significant levels of trauma exposure in more than one CTQ domain (see Table 2).

Behavioural results

One-way ANOVAs (Table 1) confirmed no group differences in task accuracy for the 'Neutral' ($p = 0.699$) and 'No-Go' ($p = 0.386$) conditions, and no difference in reaction time for the 'Neutral' condition ($p = 0.131$).

Brain imaging

The positive effect of task ('No-Go > Neutral') across the whole sample was evident in regions classically implicated in response inhibition, including bilateral dACC/mPFC, IFG/anterior insular cortex (AIC), DLPFC, IPL and striatum (Fig. 1*a*).

Regions-of-interest

The initial ROI analysis (MANOVA including all ROIs as dependent variables: left and right IFG, right DLPFC, right IPL, SMA and dACC), revealed no significant trauma-by-diagnosis interaction (Wilks' $\lambda = 0.949$; $F_{6,156} = 1.393$, $p = 0.221$; partial $\eta^2 = 0.051$) or main effect of diagnosis (Wilks' $\lambda = 0.959$; $F_{6,156} = 1.117$, $p = 0.355$; partial $\eta^2 = 0.041$), but a significant main effect of trauma exposure (Wilks' $\lambda = 0.876$; $F_{6,156} = 3.668$, $p = 0.002$; partial $\eta^2 = 0.124$). When the results for the dependent variables were considered separately, the left IFG was the only region to reach statistical significance ($F_{1,161} = 13.151$, $p < 0.001$, partial $\eta^2 = 0.076$), with trauma-exposed groups showing significantly increased activation (M = 1.137, S.E. = 0.106) relative to non-exposed groups (M = 0.607, S.E. = 0.101). Exploratory Pearson's correlation indicated that activation of the left IFG ROI was negatively associated with accuracy for the No-Go condition in non-exposed participants (independently of their clinical status; $r = 0.268$, $p = 0.022$), but not in the exposed sample ($r = -0.022$, $p = 0.838$).

In order to determine the potential interaction of diagnosis with trauma exposure, ROI analyses were repeated with diagnosis (HC, BD, SZ) included as an independent variable. There remained a significant main effect of trauma exposure (Wilks' $\lambda = 0.878$; $F_{6,154} = 3.573$, $p < 0.001$; partial $\eta^2 = 0.520$), but no significant effect of diagnosis (Wilks' $\lambda = 0.916$; $F_{12,308} = 1.157$, $p = 0.314$; partial $\eta^2 = 0.043$) and no diagnosis-by-trauma interaction (Wilks' $\lambda = 0.903$; $F_{12,308} = 1.348$, $p = 0.190$; partial $\eta^2 = 0.050$). The effect of trauma was again evident only on activation levels in the left IFG for all groups ($F_{1,159} = 12.647$, $p < 0.001$, partial $\eta^2 = 0.074$).

Psychophysiological interactions (gPPI)

The 2 × 2 ANOVAs revealed a significant main effect of trauma exposure on functional connectivity between the left IFG seed region and a cluster including the left cerebellar lobule VI, Crus I, vermis VII and fusiform gyrus, as well as with a cluster covering the right calcarine sulcus (Table 3; Fig. 1*b*). There were no other significant effects of trauma exposure, diagnosis or interaction on functional coupling with any other seed region explored (right IFG, right DLPFC, right IPL, SMA or dACC).

Antipsychotic medication and symptom severity

Pearson's correlations indicated there were no significant associations between activation in the ROIs and CPZ equivalence levels (all $p > 0.100$) in the clinical group. However, increased activation in the left IFG was associated with increased PANSS Positive ($r =$

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Table 1. Sociodemographic, clinical and behavioural data and results of comparisons among trauma subtypes

	Healthy controls ($n = 53$)		Clinical cases ($n = 112$)		Statistics		
	Non-exposed ($N = 32$)	Exposed ($N = 21$)	Non-exposed ($N = 41$)	Exposed ($N = 71$)	F/Welch/t/χ^2/Fischer's	df	p Values
Age (s.d.)	35.40 (7.61)	42.10 (12.50)	38.32 (11.66)	37.68 (11.03)	1.791	3,64.63	0.158
Gender (F/M)	15/17	8/13	20/21	43/28	4.220	3	0.239
Handedness L/A/R	1/5/26	0/2/19	0/6/35	1/10/60	2.244	6	0.896
Education (s.d.)	18.03 (2.37)	15.69 (2.84)	15.26 (2.86)	15.10 (2.82)	9.054	3,161	**<0.001**
WASI (s.d.)	116.07 (11.88)	111.33 (16.30)	110.41 (14.97)	107.30 (13.20)	3.004	3,161	**0.032**
CTQ Emotional abuse (s.d.)	6.78 (2.20)	11.05 (4.57)	7.12 (1.87)	13.85 (5.20)	38.503	3,64.30	**<0.001**
CTQ Physical abuse (s.d.)	5.88 (1.13)	8.71 (3.48)	5.39 (0.86)	9.06 (4.44)	20.295	3,62.21	**<0.001**
CTQ Sexual abuse (s.d.)	5.03 (0.18)	7.38 (2.84)	5.20 (0.56)	9.24 (5.69)	18.147	3,59.46	**<0.001**
CTQ Emotional neglect (s.d.)	8.16 (2.50)	11.00 (4.52)	8.39 (3.15)	13.52 (4.86)	21.174	3,66.53	**<0.001**
CTQ Physical neglect (s.d.)	5.94 (1.19)	7.81 (3.40)	6.34 (1.49)	6.85 (2.97)	15.517	3,65.14	**<0.001**
CTQ Total (s.d.)	31.78 (4.97)	45.95 (11.66)	32.44 (5.27)	54.31 (14.36)	55.561	3,65.69	**<0.001**
DASS depression (s.d.)	2.60 (3.67)	3.96 (4.69)	8.68 (8.77)	12.87 (10.97)	19.165	3,73.51	**<0.001**
DASS anxiety (s.d.)	2.01 (3.33)	2.67 (3.25)	9.27 (8.26)	11.83 (10.35)	23.714	3,78.62	**<0.001**
DASS stress (s.d.)	4.63 (5.80)	8.10 (7.63)	13.95 (9.97)	16.34 (11.63)	18.321	3,70.36	**<0.001**
Ratio (BD/SZA/SCZ)	–	–	19/6/16	37/14/20	1.502	2	0.472
Length of illness, years (s.d.)	–	–	16.78 (10.02)	15.06 (8.73)	0.951	110	0.344
PANSS positive (s.d.)	–	–	10.8 (3.82)	13.25 (7.60)	2.197	108.38	**0.030**
PANSS negative (s.d.)	–	–	11.07 (4.40)	13.24 (6.57)	2.084	107.49	**0.040**
PANSS general (s.d.)	–	–	22.49 (4.53)	26.77 (9.40)	3.246	107.27	**0.002**
PANSS total (s.d.)	–	–	44.44 (9.83)	53.27 (19.00)	3.237	108.96	**0.002**
MADRS (s.d.)	–	–	6.07 (5.04)	11.54 (9.40)	4.003	109.52	**<0.001**
BDRS (s.d.)	–	–	8.46 (6.16)	13.20 (8.98)	3.302	106.64	**0.001**
YMRS (s.d.)	–	–	4.68 (4.99)	7.58 (9.3)	2.144	109.50	**0.034**
Antidepressant IMI, mg (s.d.)	–	–	41.57 (113.91)	37.59 (79.10)	0.217	110	0.828
Antipsychotic CPZ, mg (s.d.)	–	–	223.37 (242.05)	531.91 (1149.75)	2.179	80.33	**0.032**
Mood stabilizers, n (Y/N)	–	–	19/22	34/37	0.025	1	1.000
Neutral accuracy % (s.d.)	98.08 (5.55)	98.31 (4.52)	95.99 (11.38)	96.68 (10.20)	0.477	6,161	0.699
Neutral RT, ms (s.d.)	716.19 (142.00)	711.39 (150.82)	746.38 (136.39)	761.98 (163.26)	1.019	6,161	0.386
No-Go accuracy % (s.d.)	94.79 (6.31)	93.51 (7.00)	92.61 (6.06)	90.70 (11.06)	1.941	3,69.28	0.131

df, degrees of freedom; s.d., standard deviation; BD, bipolar-I disorder; SZA, schizoaffective disorder; SCZ, schizophrenia; L/A/R, left handed, ambidextrous or right handed; WASI, Wechsler abbreviated scale of intelligence; CTQ, childhood trauma questionnaire; DASS, depression, anxiety and stress scale; PANSS, positive and negative syndrome scale; MADRS, Montgomery-Åsberg depression rating scale; BDRS, bipolar depression rating scale; IYMRS, Young mania rating scale; IMI, mean imipramine dosage equivalent in milligrams; CPZ, mean chlorpromazine dosage equivalent in milligrams; RT, reaction time in milliseconds. Significant group differences are in bold

Table 2. Number and type of CTQ domains endorsed by BD, SZ and HC groups

	Exposed BD ($n = 37$)	Exposed SZ ($n = 34$)	Exposed cases ($n = 71$)	Exposed HC ($n = 21$)
CTQ Emotional abuse, *n*	24 (65%)	17 (50%)	41 (54%)	7 (33%)
CTQ Physical abuse, *n*	12 (32%)	13 (38%)	25 (32%)	10 (48%)
CTQ Sexual abuse, *n*	16 (43%)	17 (50%)	33 (51%)	10 (48%)
CTQ Emotional neglect, *n*	17 (46%)	12 (35%)	29 (43%)	4 (19%)
CTQ Physical neglect, *n*	11 (30%)	15 (44%)	26 (38%)	5 (24%)
CTQ domains within moderate to extreme range				
1 CTQ domain, *n*	15 (41%)	14 (41%)	29 (41%)	12 (57%)
2 CTQ domains, *n*	8 (22%)	7 (21%)	15 (21%)	5 (24%)
3 CTQ domains, *n*	8 (21%)	8 (23%)	16 (23%)	2 (10%)
4 CTQ domains, *n*	5 (13%)	3 (9%)	8 (11%)	2 (9%)
5 CTQ domains, *n*	1 (3%)	2 (6%)	3 (4%)	0
Number of cases reporting each domain of CTQ uniquely				
CTQ Emotional abuse, *n*	7 (19%)	2 (6%)	9 (13%)	1 (5%)
CTQ Physical abuse, *n*	1 (3%)	1 (3%)	2 (3%)	4 (19%)
CTQ Sexual abuse, *n*	6 (16%)	5 (15%)	11 (15%)	5 (24%)
CTQ Emotional neglect, *n*	1 (3%)	4 (12%)	5 (7%)	1 (5%)
CTQ Physical neglect, *n*	0	2 (6%)	2 (3%)	1 (5%)

CTQ, childhood trauma questionnaire; BD, bipolar I disorder; SZ, schizophrenia/schizoaffective disorder; HC, healthy participants.

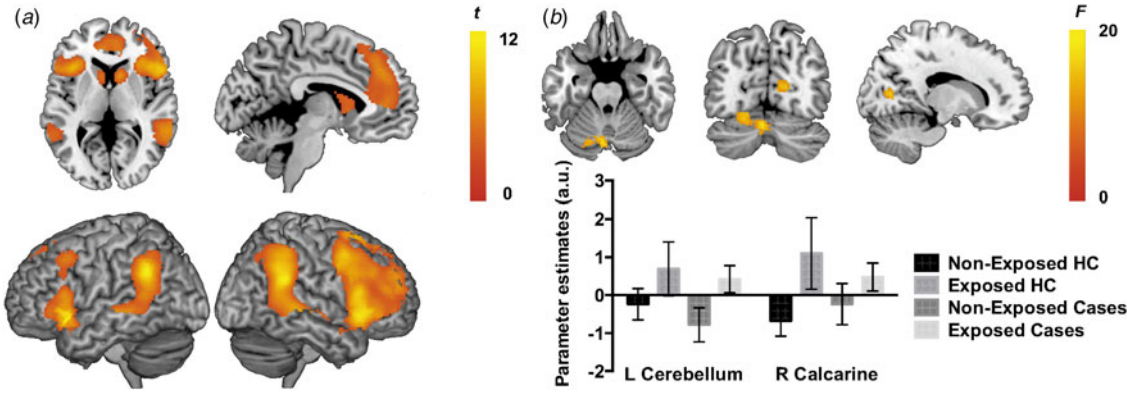

Fig. 1. Positive effect of task (*a*) and main effect of childhood trauma exposure on functional connectivity with the left inferior frontal gyrus (IFG) seed region (*b*). Colour bar represents *F*- or *t*-values values; error-bars represent 95% confidence interval; a.u.: arbitrary unit; initial $p<0.001$ uncorrected, with cluster-wise family-wise error (FWE) correction [p(FWEc) = 0.05].

0.189, $p = 0.046$) and PANSS General symptomatology ($r = 0.228$, $p = 0.016$), but not with PANSS Negative symptoms ($r = 0.166$, $p = 0.080$).

Mediation analyses

The first model investigated the potential role for left IFG activation to mediate the effects of trauma on general symptom severity (Fig. 2*a*). We identified significant associations between key variables, as represented in (1) *path a*: the association between trauma exposure and left IFG activation ($\beta = 0.35$, S.E. = 0.17, $t_{110} = 2.01$, $p < 0.05$); (2) *path b*: the association between left IFG activation during response inhibition and PANSS general symptoms ($\beta = 1.72$, S.E. = 0.85, $t_{109} = 2.35$, $p = 0.02$), but not PANSS positive ($\beta = 1.19$, S.E. = 0.70, $t_{109} = 1.71$, $p = 0.09$) or negative symptoms ($\beta = 0.91$, S.E. = 0.63, $t_{109} = 1.45$, $p = 0.15$), and; (3) path c': the direct effect of trauma exposure on PANSS general symptoms ($\beta = 3.69$, S.E. = 1.57, $t_{110} = 2.35$, $p = 0.02$), but not PANSS positive ($\beta = 1.96$, S.E. = 1.28, $t_{110} = 1.53$, $p = 0.13$) or negative symptoms ($\beta = 1.85$, S.E. = 1.17, $t_{110} = 1.58$, $p = 0.12$). After controlling for left IFG activation, trauma remained a significant predictor of general symptom severity (path c': $\beta = 3.69$, S.E. = 1.57, $t_{109} = 2.74$, $p = 0.02$), indicating that activation levels in the left IFG during response inhibition is not a significant mediator of the effects of trauma exposure on general symptom severity.

The second model tested the role of general symptom severity on mediating the effects of trauma on activation in the left IFG. We identified significant associations between key variables, as

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Table 3. Peaks of clusters showing significant main effect of trauma exposure on functional connectivity with the left IFG seed region revealed by between group 2 (trauma: exposed/non-exposed) × 2 (diagnosis: cases/HC) ANOVA during response inhibition

Hem	Cluster region	BA	MNI Coordinates			Cluster size (voxels)	Peak *F*-statistics	Peak *z*-scores	Cluster *p* (FWEc)
			x	*y*	*z*				
Main effect of trauma									
L	Cerebellum (Lobule VI;	19	**−4**	**−72**	**−24**	**264**	**19.13**	**4.09**	**<0.0001**
	Crus I; Vermis VII)		−20	−70	−16		18.90	4.06	
	Fusiform gyrus		−12	−68	−20		15.04	3.61	
R	Calcarine sulcus	17/18/23/30	**14**	**−70**	**8**	**235**	**17.64**	**3.92**	**<0.0001**
			4	−90	4		17.06	3.85	
			6	−90	0		16.37	3.77	

Hem, hemisphere; L, left; R, right; BA, Brodmann area; MNI, Montreal Neurologic Institute; FWEc, family-wise error correction for multiple comparisons at the cluster level; IFG, inferior frontal gyrus.
Main peaks within the cluster of interest are in bold.

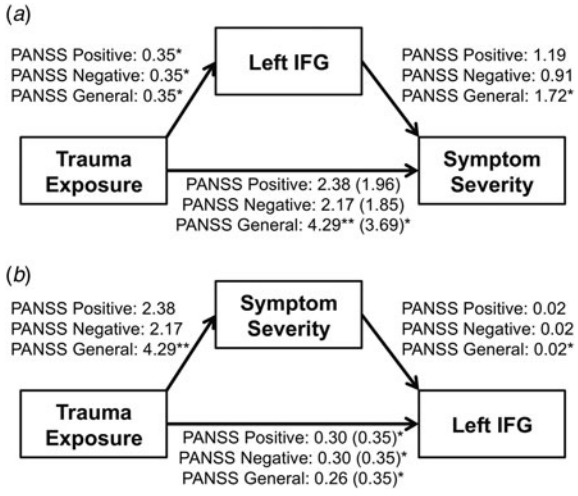

Fig. 2. Mediation analyses. (*a*) Mediation effects of left inferior frontal gyrus (IFG) activation during response inhibition on the effects of trauma exposure on levels of psychopathology as measured by the PANSS. (*b*) Effects of symptom severity on the effects of trauma exposure on activation of the left IFG. *$p < 0.05$; **$p < 0.01$.

represented in (1) path *a*: the association between trauma exposure and PANSS general symptoms ($\beta = 4.29$, S.E. = 1.56, $t_{110} = 2.74$, $p < 0.01$), but not PANSS positive ($\beta = 2.38$, S.E. = 1.27, $t_{110} = 1.87$, $p = 0.06$) or negative symptoms ($\beta = 2.17$, S.E. = 1.15, $t_{110} = 1.88$, $p = 0.06$); (2) path *b*: the association between PANSS general symptoms and IFG activation during response inhibition ($\beta = 0.02$, S.E. = 0.01, $t_{109} = 2.02$, $p < 0.05$), but not PANSS positive ($\beta = 0.02$, S.E. = 0.01, $t_{109} = 1.71$, $p = 0.09$) or negative symptoms ($\beta = 2.17$, S.E. = 0.01, $t_{109} = 1.45$, $p = 0.09$), and; (3) path *c*′: the direct effect of trauma exposure on activation in the left IFG ($\beta = 0.35$, S.E. = 0.17, $t_{110} = 2.01$, $p < 0.05$). Because only PANSS general symptoms were associated with both trauma exposure and brain function, mediation was formally tested for this variable only. Trauma exposure was no longer a significant predictor of task-related activation of the left IFG after controlling for PANSS general symptom severity (path *c*′: $\beta = 0.26$, S.E. = 0.18, $t_{109} = 1.47$, $p = 0.15$), consistent with partial mediation. General symptom severity accounted for over a quarter of the variance in left IFG activation ($P_M = 0.26$). The indirect effect of trauma exposure on IFG was tested using a bootstrap estimation approach with 10 000 samples. These results indicated that the indirect coefficient was significant ($a.b = c–c' = 0.09$, S.E. = 0.06, 95% CI 0.004–0.23). Trauma exposure was thus associated with a 9% increased activation in the left IFG during response inhibition in psychosis cases, mediated by general symptom severity (see Fig. 2*b*).

Discussion

This study identified increased levels of activation in the left IFG in association with childhood trauma exposure during response inhibition, regardless of clinical diagnostic status, and in the context of equivalent behavioural performance across clinical and health groups. There was no main effect of diagnosis with schizophrenia, and no interaction of trauma with diagnosis for any ROI (right IFG, right DLPFC, right IPL, SMA and dACC). In addition, increased functional connectivity between the left IFG seed region (only) and both cerebellar and calcarine regions were evident as a main effect of trauma exposure. Finally, mediation analyses within the clinical sample indicated that the effect of trauma on left IFG activation was mediated by the severity of the PANSS general psychopathology scores. However, left IFG activation did not mediate the effect of trauma exposure on PANSS general psychopathology scores.

In the context of equivalent behavioural performance, trauma-related increased activation within the left IFG suggests that stronger signals of salience from the left IFG may be required to adequately inhibit motor responses to the target stimulus. This is consistent with findings observed for a Stop-signal task in adolescents exposed to early-life stress (Mueller *et al.* 2010), and the known role of the IFG, together with the AIC and the dACC, within the so-called salience network (which designates and responds to task-relevant events/stimuli) (Uddin, 2015). In addition to salience signalling, the IFG/AIC is critical for adequate cognitive control functions including response inhibition (Criaud & Boulinguez, 2013; Aron *et al.* 2014). While the right IFG is generally associated with response inhibition (Criaud & Boulinguez, 2013; Aron *et al.* 2014), the left IFG is more specifically associated with successful inhibition of motor response (Swick *et al.* 2008; Boehler *et al.* 2010; Gu *et al.* 2013), in line with the present findings. An alternative explanation might

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implicate functional compensatory mechanisms arising from trauma-related grey matter loss in the IFG, as has been reported elsewhere (Lim *et al.* 2014). The relationship between trauma-related structural and functional abnormalities in this region will need to be explicitly investigated in future studies using a multi-modal imaging approach in the same participants.

That the severity of general symptoms was a significant mediator of the effects of trauma exposure on left IFG function in the clinical group is perhaps not surprising given that trauma-exposed psychosis cases often present with greater levels of symptom severity (Duhig *et al.* 2015). Moreover, general symptoms were recently shown to mediate the effects of childhood trauma on both positive and negative symptoms in schizophrenia (Isvoranu *et al.* 2017). Importantly, only partial mediation was observed in the present study, indicating that other, unmeasured factors might play a role in mediating these effects. For example, given the emerging relationships between childhood trauma exposure, and psychotic and posttraumatic stress symptoms (Hardy *et al.* 2016; Powers *et al.* 2016), PTSD phenomena may play a crucial role in this model. Future studies might therefore consider the use of comprehensive interviews to index PTSD symptoms for investigation in this context. The results also suggest that relevant trauma-focused treatments for psychosis patients reporting significant levels of childhood adversity, such as eye-movement desensitization and reprocessing (EMDR) or prolonged exposure therapy (van den Berg *et al.* 2015), might assist in reducing anxiety or depressive symptoms.

Rather unexpectedly, trauma-exposure was also associated with increased connectivity between the left IFG seed and both primary visual regions (calcarine sulcus) and cerebellar (lobule VI, crus I) regions; these latter regions are essential for executive functions (Stoodley & Schmahmann, 2009) and are involved in event timing (Keren-Happuch *et al.* 2014). A plausible explanation may be that trauma-exposed individuals need greater inputs from these regions to rapidly integrate salient, task-relevant indices for accurate inhibition of motor response (equivalent levels of task performance) compared with non-exposed individuals. However, this interpretation remains speculative and requires further investigation using effective connectivity or independent component analyses to identify functional networks of brain regions impacted by psychosis and/or trauma exposure.

Finally, the absence of behavioural differences in response inhibition may also explain the lack of trauma- and/or psychosis-related differences in other brain regions classically implicated in cognitive (DLPFC, dACC and IPL) and sensorimotor (SMA) controls, as previously reported in schizophrenia (Sambataro *et al.* 2013). The chronic nature of illness experienced by most of the patients [mean illness length (S.D.) = 15.69 (9.22) years], who had likely been taking medications to stabilize symptoms for much of this time, may have contributed to this observation. These drugs have long-term effects on grey matter integrity (Moncrieff & Leo, 2010; Ho *et al.* 2011; van Haren *et al.* 2011; Fusar-Poli *et al.* 2013) that also influence brain function (Abbott *et al.* 2013), in particular in cortical dopaminergic target regions, such as DLPFC and ACC.

The present findings should be considered in light of the following limitations. First, we were unable to investigate the specific effects of any one type of trauma without potential contamination of the effects of other types of trauma because of the high rate of exposure to more than one type of abuse or neglect (see Table 2). Second, while endorsed elsewhere (Shannon *et al.* 2011; Mørkved *et al.* 2017), the use of moderate to extreme range CTQ scores to define significant levels of trauma-exposure may be conservative, and/or may inappropriately lump together individuals who have experienced maltreatments of a different nature. Third, consistent with the chronic illness state of our clinical sample, medication use may have affected our results; the potential effects of specific types of medication were investigated statistically where possible, but the possibility of general effects on brain function cannot be completely ruled out and may have, at least partly contributed to the lack of main effect of psychosis and psychosis-by-trauma interaction on brain function. Finally, posttraumatic stress symptoms were not assessed here. Because positive symptoms may also be considered as trauma intrusions (Morrison, 2001), it will become important to include these measures to better understand the effects of childhood trauma in psychosis (Alsawy *et al.* 2015; Powers *et al.* 2016).

In conclusion, this study provides evidence for the impact of childhood trauma on the left IFG function during cognitive inhibition in adult patients diagnosed with schizophrenia, schizoaffective disorder or bipolar I disorder, as well as in healthy individuals. Exposure to childhood trauma was not associated with poor behavioural performance, but was associated with greater activation and increased task-related functional connectivity with the left IFG, suggestive of heightened salience signalling required for adequate response inhibition. Importantly, these trauma-related findings were mediated by symptom severity in psychosis cases. Future investigations are required to better understand the long-term implications of the exposure to childhood trauma on other domains of executive function, in particular conflict monitoring and attention.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291717002884.

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Declaration of Interest. All of the authors declare that they have no conflicts of interest.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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