Schizophrenia Research 110 (2009) 47–58

Contents lists available at ScienceDirect

Schizophrenia Research

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

Neural and behavioural responses to threat in men with a history of serious violence and schizophrenia or antisocial personality disorder

Veena Kumari [a,b,*], Mrigendra Das [c,d], Pamela J. Taylor [e], Ian Barkataki [c], Christopher Andrew [f], Alexander Sumich [a,f], Steven C.R. Williams [f], Dominic H. ffytche [f]

[a] Department of Psychology, Institute of Psychiatry, King's College London, London, UK
[b] NIHR Biomedical Research Centre for Mental Health, South London and Maudsley NHS Trust, London, UK
[c] Division of Psychological Medicine and Psychiatry, Institute of Psychiatry, King's College London, London, UK
[d] Broadmoor Special Hospital, Crowthorne, Berkshire, UK
[e] Department of Psychological Medicine, School of Medicine, Cardiff University, Cardiff, UK
[f] Centre for Neuroimaging Sciences, Institute of Psychiatry, King's College London, London, UK

ARTICLE INFO

Article history:
Received 18 August 2008
Received in revised form 7 January 2009
Accepted 10 January 2009
Available online 20 February 2009

Keywords:
Schizophrenia
fMRI
Fear
Threat
Serious violence
Antisocial personality disorder

ABSTRACT

Background: Contemporary theories and evidence implicate defective emotion regulation in violent behaviour. The two psychiatric illnesses most implicated in violence are schizophrenia and antisocial personality disorder (APD). This study examined behavioural and brain abnormalities in violent men with schizophrenia or APD during anticipatory fear.
Method: Fifty-three men [14 non-violent healthy controls, 13 with schizophrenia and a history of serious violence (VSZ), 13 with schizophrenia without a history of violence (SZ), 13 with APD and a history of serious violence] underwent blood-oxygenation-level-dependent fMRI during an experiment involving repeated presentations of 'safe' and 'threat of electric shock' conditions and provided ratings of shock anticipation and fear. Schizophrenia patients did not have co-morbid APD.
Results: VSZ participants reported the highest, and APD participants the lowest, level of shock anticipation and fear, with intermediate ratings by SZ and healthy participants. The violent, relative to non-violent, groups showed altered activity modulation in occipital and temporal regions, from early to latter parts of threat periods. Additionally, VSZ patients displayed exaggerated whereas APD patients showed attenuated thalamic-striatal activity during latter threat periods.
Conclusions: Aberrant activity in occipital and temporal regions when exposed to sustained visual threat cues is associated with a predisposition to violence in both schizophrenia and APD. This common biological deficit, however, appears to arise from dissimilar behavioural mechanisms related to differences in the strength of aversive conditioning and behavioural response to sustained threat cues (enhanced in VSZ; attenuated in APD), also reflected in opposite patterns of alternations in thalamic-striatal activity, in these two disorders.

1. Introduction

Violent behaviour is associated with certain mental disorders, most markedly schizophrenia (Arseneault et al., 2000) and antisocial personality disorder (APD) (Hodgins, 1992). Although positive symptoms may drive inpatient violence, several other factors contribute on their own or in interaction with symptoms to persistent violence in the community shown by schizophrenia patients (Krakowski, 2005).

Dysfunction within a neural circuit implicated in emotion regulation is considered to constitute the neural substrates of violence (Davidson et al., 2000). This circuit includes several

* Corresponding author. PO78, Department of Psychology, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK. Tel.: +44 207 848 0233; fax: +44 207 848 0860.
E-mail address: v.kumari@iop.kcl.ac.uk (V. Kumari).

0920-9964/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.schres.2009.01.009

regions of the prefrontal cortex, amygdala, hippocampus, hypothalamus, anterior cingulate (AC), striatum and other interconnected structures (Davidson et al., 2000). Behaviourally, schizophrenia patients with a history of violent behaviour show a better ability to identify facial emotional expressions but a poorer ability to discriminate between intensity of emotions compared to non-violent schizophrenia patients (Silver et al., 2005). Schizophrenia patients with high psychopathy scores show impaired recognition of sadness at low intensity compared to those with low psychopathy scores (Fullam and Dolan, 2006). Despite the vast literature showing cortico-limbic abnormalities during processing of affective information (e.g. Gur et al., 2002; Williams et al., 2004), previous studies have not examined functional brain abnormalities using an affective processing paradigm in association with persistent violent behaviour in schizophrenia.

There is reliable evidence of impaired ability to anticipate punishment, reduced psychophysiological responsiveness to threatening events, and reduced experience of aversive states in individuals with high psychopathic traits who form part of a wider group of people with APD (review, Herba et al., 2004). Studies of psychopathic/APD individuals suggest that altered functions mainly of regions located within the frontal and temporal lobes, that are implicated in response inhibition, modulation of aggressive or submissive behaviour, recognition of expressions of fear and anger, and fear conditioning, are involved in mediation and expression of psychopathy and antisocial behaviour (reviews, Herpertz and Sass, 2000; Dolan, 2002; Herba et al., 2004; Kumari and Taylor, In press). Event-related potentials and imaging studies of psychopathic individuals by Kiehl and colleagues have shown paralimbic dysfunction and associated behavioural abnormalities in psychopathy (review, Kiehl, 2006).

In this study we examined neural dysfunctions, measured with functional magnetic resonance imaging (fMRI), associated with a history of serious physical violence during an anticipatory fear paradigm (Chua et al., 1999; Kumari et al., 2007) in schizophrenia. We also studied a group with APD and a history of similar level of violence to that in patients with schizophrenia to elucidate common and distinct brain correlates of violence in these two disorders. We hypothesized, albeit with limited confidence given the lack of relevant imaging data in schizophrenia, that both violent groups would show altered fronto-temporal activity. We also predicted that our experimental manipulation involving an aversive procedure would be the least effective in violent APD individuals.

2. Materials and methods

2.1. Participants and design

We used a cross-sectional design, involving four groups: (i) 14 healthy men (HC) with no history of violence or a mental disorder, (ii) 13 men with schizophrenia with no history of violence (SZ), (iii) 13 men with schizophrenia and a history of serious violence (VSZ), and (iv) 13 men with APD and a similar history of violence to that of VSZ.

VSZ and APD patients were recruited from specialist high and medium security hospitals which provide treatment and security for people with mental disorders who are subject to compulsory detention because of their dangerous, violent or criminal propensities. Most of them had extensive violence histories before admission to a secure hospital. SZ patients were recruited from local hospitals or outpatient clinics and included only if they did not have a history of violent behaviour, verified at interview and by clinical record screen. HC were recruited via local advertisements and screened for a history of mental illness (Spitzer et al., 1990). The sample was recruited as part of a larger project (Kumari et al., 2006; Narayan et al., 2007).

All included participants were aged between 18 and 55 years, free of substance abuse (confirmed by urine analysis), neurological conditions or head injury, and spoke English as their first language. SZ and VSZ patients had a diagnosis of schizophrenia (First et al., 1995) but no co-morbid diagnosis of APD (First et al., 1997). APD patients had a diagnosis of APD (cluster B, DSM IV) but no co-morbid diagnosis of schizophrenia. Among the schizophrenia groups, diagnosis included paranoid (9 SZ, 10 VSZ), undifferentiated (2 SZ, 3 VSZ), disorganised (1 SZ) and residual (1 SZ) subtypes. Within the APD group, 8 patients had co-morbid antisocial and borderline personality disorders, 3 had co-morbid antisocial, borderline and paranoid personality disorders, 1 had antisocial, borderline and histrionic personality disorders, and 1 had antisocial personality disorder without other co-morbid disorders. All VSZ and APD had been free of alcohol and substance misuse for a minimum of two years (confirmed by regular random urine screens in secure hospitals).

The study procedures were approved by relevant local ethics committees. All participants provided written informed consent.

2.2. Assessment of violence

The history of violence (or a lack of it) was established using clinical and forensic records (where appropriate). It is sometimes a matter of chance whether criminal proceedings are pursued; the level of harm done to the victim of an assault can also depend on a range of factors other than the nature of the assault itself. In order to minimise these distortions, research ratings of violence were made according to the Gunn–Robertson scale (score range 0–8) (Gunn and Robertson, 1976) based on the frequency of serious violence over lifetime (score 0–4) and the severity of the most recent violence act (score 0–4). A cut-off of 5 was used for inclusion in the violent groups, indicative of an index fatal or near fatal act of violence against another and at least one other episode of at least moderately serious violence. Any evidence of actual violence against another person, whether or not it had led to a criminal conviction was taken as an exclusion criterion for HC and SZ groups.

2.3. Other assessments

In all patients with schizophrenia, symptoms were rated using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). The PANSS is a popular semi-structured interview consisting of a 30-item, 7-point severity scale [1 (absence of psychopathology) to 7 (extremely severe)]. It assesses a wide range of symptoms of schizophrenia, yielding 'positive', 'negative' and 'general psychopathology' symptom sub-scales. The 5-factor model of PANSS (Lindenmayer et al., 1995) examines 'positive', 'negative', 'cognitive', 'excitement' and 'depression' syndromes.

The type and doses of current antipsychotic treatment were recorded for all patients with schizophrenia for sample characterization purposes. No APD patient was on any psychotropic medication. For all participants, previous substance and alcohol misuse/dependency details were obtained from clinical and forensic records and interview with the participant.

Predicted intelligence (IQ) was assessed in all participants using the National Adult Reading Test (NART; Nelson and Willison, 1991). The NART requires participants to read 50 irregularly spelled words (e.g. debt, catacomb) in order of increasing difficulty. These words do not follow the normal rules of grapheme–phoneme representation and can only be correctly pronounced with prior knowledge. The NART is assumed to measure premorbid IQ (i.e. the level of intellectual ability prior to the onset of a disorder or a brain legion) since the word-reading ability correlates highly (0.75) with IQ in healthy people (Nelson and McKenna, 1975) and is remarkably preserved in dementing patients with cognitive deterioration (Nelson and O'Connell, 1978). Previous studies have shown than the NART provides a valid estimate of premorbid IQ in patients with schizophrenia (e.g. O'Carroll et al., 1992; Bright et al., 2002). The NART has also been used to assess predicted IQ in individuals with APD (Dolan and Park, 2002).

2.4. Experimental paradigm and procedure

The paradigm involved repeated presentation of a 'safe' (control) condition for 30 s followed by presentation of a 'threat of shock' (experimental) condition for 30 s The safe-shock cycle was presented 5 times during the course of the experiment. The chosen experimental design and stimulus parameters were based on previous studies utilizing similar procedures to successfully potentiate amplitude of the human acoustic startle response indicating fear elicitation (e.g. Grillon et al., 1994).

Before going into the scanner, a mild electric shock was delivered to participants transcutaneously over the left median nerve by a stimulating bar electrode. The electrode leads were attached by a velcro strap positioned near their wrist and attached to a Digitimer DS7A stimulator which was used to deliver the electric shock. Participants were told that while lying in the scanner, they would see 'shock' and 'safe' conditions, displayed on the screen and that they may be delivered one or more shocks of similar or stronger intensity than the one received outside during one/more of the shock conditions, but no shocks would be delivered during the safe conditions. In reality, participants did not receive any shock while in the scanner. The experimental design was kept simple, given the involvement of difficult clinical groups.

After the scanning, all participants were debriefed and ratings were taken using 100-mm visual analogue scales on the level of fear (from safe-to-most fearful) experienced while inside the scanner during the safe and threat periods and the level of belief/anticipation (not at all anticipated-to-most anticipated) that shocks would be delivered when indicated by the word 'shock' on the screen.

2.5. Image acquisition

Echoplanar MR brain images were acquired using a 1.5 T GE Signa system (General Electric, Milwaukee WI, USA). In each of 16 near-axial non-contiguous planes parallel to the inter-commissural (AC–PC) plane, 100 T2*-weighted MR images depicting blood-oxygenation-level-dependent (BOLD) contrast

Table 1
Demographic, clinical and behavioural characteristics of participant groups.

Demographic/clinical measures		HC Mean (SD)	SZ Mean (SD)	VSZ Mean (SD)	APD Mean (SD)	*F* group	*df*	*p*
Age		33.14 (6.6)	34.31 (7.3)	34.46 (4.94)	32.85 (10.57)	0.15	3, 49	0.929
Premorbid IQ[a]		107.36 (16.54)	98.85 (14.43)	96.38 (13.93)	96.85 (9.91)	1.83	3,49	0.154
Violence variables								
Violence score[b]		0.54 (0.88)	1.38 (1.32)	6.15 (1.46)	6.77 (1.16)	88.6	3, 49	<0.001
Index offence				5 homicide 2 attempted murder 4 wounding 2 interpersonal violence	5 homicide 3 attempted murder 3 wounding 2 interpersonal violence			
Schizophrenia variables								
Age of onset (years)			22.92 (5.34)	22.31 (6.70)		0.06	1,24	0.77
Duration of illness (years)			11.31 (7.86)	12.15 (7.32)		0.08	1,24	0.77
Positive symptoms[c]			12.38 (4.09)	11.00 (5.57)		0.52	1,24	0.48
Negative symptoms[c]			20.23 (5.68)	18.15 (5.67)		0.87	1,24	0.36
General psychopathology[c]			33.69 (5.56)	25.36 (6.02)		12.40	1,24	0.002
Chlorpromazine equivalents (mg/day)			567.00 (323.52) (9 atypical and 4 typical antipsychotics)	426.67 (227.61) (9 atypical and 4 typical antipsychotics)		1.42	1, 20	0.247
Behavioural measures (0–100 mm)								
Fear	Safe	20.53(26.57)	19.38(22.89)	23.69(32.77)	12.77(20.53)	1.537	3,49	0.217
	Shock	48.57(36.28)	51.85(32.69)	66.61(28.42)	38.23(27.27)			
Shock Anticipation		71.42(24.01)	77(17.46)	86.92(8.85)	54.31(30.04)	5.19	3,49	0.003

[a]Assessed with the National Adult Reading Test; [b]Gunn and Robertson Scale; [c]Positive and Negative Syndrome Scale.

Table 2
Peaks and sub-peaks of regions showing significant increases and decreases during the threat of shock conditions, relative to the safe condition, and from Shock-I to Shock-II conditions, across all participants ($n = 53$, height threshold $p = 0.001$).

Brain region	Brodmann area	MNI coordinates			Voxel *T* value	Cluster size	Cluster *p* corrected for multiple comparisons
2a. Activations							
Shock-I>Safe		*X*	*Y*	*Z*		Voxels	
Insula	n/a	38	24	−8	11.22	2610	<0.001
Inferior frontal gyrus	47	50	18	−8	10.04		
	44	50	18	26	4.52		
Anterior cingulate	24/32	2	28	38	7.75	1503	<0.001
Inferior frontal gyrus	6	6	16	60	7.20		
	8	2	30	48	5.95		
Insula	n/a	−40	20	−2	7.34	1343	<0.001
Orbitofrontal gyrus	11	−46	24	−18	4.14		
Inferior parietal cortex	40	−60	−50	38	7.24	504	0.003
	40	−60	−32	28	4.69		
Middle frontal gyrus	10	40	50	20	6.23	768	<0.001
	10	40	58	4	5.03		
	9	32	42	34	4.94		
Thalamus	n/a	12	−2	6	5.97	1174	<0.001
	n/a	−10	−4	6	5.83		
	n/a	4	−12	14	4.74		
Inferior parietal cortex	40	62	−32	26	5.56	1183	<0.001
	40	58	−44	34	5.47		
	40	58	−52	44	4.29		
Lingual gyrus	18	20	−82	−8	5.19	497	0.004
Cerebellum	n/a	28	−72	−26	5.17		
Occipital gyrus	18	18	−100	−2	4.57		
Cerebellum	n/a	−30	−76	−26	4.58	290	0.034
	n/a	−16	−82	−26	4.15		
Shock-II>Safe							
Insula	n/a	46	22	−8	8.13	2122	<0.001
Inferior frontal gyrus	44	54	16	14	4.75		
	44	58	20	26	4.69		
Medial frontal gyrus	6	2	24	58	6.74	1311	<0.001
	8	0	40	50	5.08		
Anterior cingulate	32	2	34	40	5.06		
Inferior parietal cortex	40	56	−52	46	5.84	2266	<0.001
	40	58	−36	24	5.64		
	40	62	−54	36	5.42		
	40	−58	−50	38	5.63	501	0.004
	40	−62	−56	24	4.41		
Superior temporal gyrus	22	−62	−54	14	3.99		
Middle temporal gyrus	21	−60	−26	−6	4.72	321	0.028
	21	−66	−38	−6	3.98		
	21	−64	−52	−6	3.80		
Insula	n/a	−40	22	−6	4.52	288	0.041
Inferior frontal gyrus	45	−50	20	4	3.84		
2b. Deactivations							
Safe>Shock-I							
Precentral gyrus	4	−44	−24	66	9.04	11,229	<0.001
	4	−38	−30	56	8.06		
	6	−8	−38	64	7.80		
Parahippocampal gyrus	35/36	−24	−42	−16	7.39	2940	<0.001
Posterior cingulate	30/23	12	−56	20	6.07		
Parahippocampal gyrus	28/35/36	30	−36	−22	6.07		
Inferior temporal gyrus	37	46	−68	0	6.80	1661	<0.001
Middle temporal gyrus	39	48	−68	24	5.12		
Occipital gyrus	19	38	−84	26	4.98		
Superior parietal cortex	7	32	−54	62	5.10	309	0.027
	7	26	−68	60	3.58		
	7	26	−54	46	3.47		
Safe>Shock-II							
Parahippocampal gyrus	30	−14	−44	4	7.30	689	0.001
Lingual gyrus	19	−24	−54	−2	3.69		
	19/18	10	−68	0	5.75	1510	<0.001
Posterior cingulate	30/23	14	−50	8	5.32		
Parahippocampal gyrus	30	18	−36	4	4.61		
Medial frontal gyrus	10	−6	46	−2	5.47	547	0.003
	10	4	48	−6	4.77		
	10	14	40	−2	4.05		

Table 2 (*continued*)

Brain region	Brodmann area	MNI coordinates			Voxel *T* value	Cluster size	Cluster *p* corrected for multiple comparisons
Safe>Shock-II							
Precentral gyrus	4	−44	−26	66	5.36	325	0.027
	4	−36	−36	70	4.18		
Precuneus	7	16	−78	54	5.26	447	0.008
	7	20	−74	38	4.11		
Precentral gyrus	4	−58	−18	48	4.88	371	0.016
	4	−52	−14	30	4.56		
	6	−40	−10	16	4.01		
Precuneus	7	−8	−52	68	4.20	291	0.039
	7	−14	−72	48	3.76		
	7	−8	−62	56	3.60		
2c. Activation changes between Shock-1 and Shock-II							
Shock-I >Shock-II							
Insula	n/a	44	26	−2	5.72	530	0.002
	n/a	52	16	−6	4.68		
	n/a	−52	12	−2	5.23	534	0.002
	n/a	−42	18	−2	4.51		
Thalamus	n/a	−4	−20	22	5.03	286	0.027
Anterior cingulate	32	4	22	36	4.14	277	0.030
	32	4	32	30	4.04		
Shock-I<Shock-II							
Medial frontal gyrus	6	−6	−30	64	8.61	5951	<0.001
	6	4	−30	64	6.97		
Precentral gyrus	4	−42	−22	60	6.44		
Middle temporal gyrus	21/37	50	−68	4	6.98	1463	<0.001
	39	50	−68	28	6.09		
Superior occipital gyrus	19	32	−76	34	4.00		
Posterior cingulate	31	10	−54	26	5.75	554	0.001
	31	−2	−62	28	4.86		
	31	−2	−48	38	3.31		
Middle occipital gyrus	19	−42	−80	12	5.70	1655	<0.001
	19	−28	−80	34	5.52		
Middle-superior temporal gyrus	39	−48	−62	28	4.47		

MNI: Montreal Neurological Institute.

(Ogawa et al., 1990) were acquired over the entire experiment with echo time (TE) = 40 ms, repetition time (TR) = 3 s, in-plane resolution = 3.1 mm, slice thickness = 7.0 mm, interslice gap = 0.7 mm. In the same session, a high-resolution inversion recovery echoplanar image (TE = 74 ms, TI = 180 ms, TR = 16 s) with an in-plane resolution of 1.5 mm and 3-mm slice thickness, 0.3 mm slice gap, was also acquired.

2.6. Statistical analysis

2.6.1. Sample characteristics and behavioural measures

Group differences in demographic and clinical variables were examined using one-way analysis of variance (ANOVA). Self-ratings of fear were analysed by a 4 (Group) × 2 (Condition: shock, safe) ANOVA with Group as the between-subjects factor and Condition as the within-subjects factor, followed by post-hoc mean comparisons (LSD method). Shock anticipation ratings were examined by a one-way (Group) ANOVA followed by post-hoc comparisons (LSD). All analysis were conducted using SPSS v15 with level of significance maintained at $p = 0.05$ unless indicated otherwise.

2.6.2. fMRI

For each participant, the 100 volume functional time series was motion corrected, transformed into stereotactic space, spatially smoothed with a 8 mm FWHM Gaussian filter and band pass filtered using statistical parametric mapping software (SPM2; http://www.fil.ion.ucl.ac.uk/spm).

Data were analysed using a two-stage random effect procedure. For the purpose of fMRI data analysis, the shock (experimental) condition within each of the five 30-s blocks was divided into two parts (shock-I: first 9 s, shock-II: last 21 s) mainly because we considered the possibility of amygdala activation and the observation that amygdala activity may habituate very quickly after the initial processing of the aversive warning stimulus (Buchel et al., 1998). Subject-specific activations were identified with a model consisting of two experimental conditions (shock-I, shock-II) and the safe condition as an implicit baseline. The boxcar for each epoch was convolved with the haemodynamic response function. The generic activations across all participants for shock-I and shock-II relative to safe condition, and relative to each other, were identified using one-sample t-tests performed on relevant contrast images (height threshold $p = 0.001$; corrected for multiple comparisons at the cluster level $p < 0.05$).

We performed ANOVAs within SPM on shock-I and shock-II versus safe images, and shock-I versus shock-II images, with Group as the between-subjects factor to identify regions (height threshold $p = 0.01$, corrected for multiple comparisons at the cluster level $p < 0.05$) differentiating two or more groups using planned contrasts [violent groups (VSZ, APD) against the non-violent groups (SZ, HC); each of the clinical

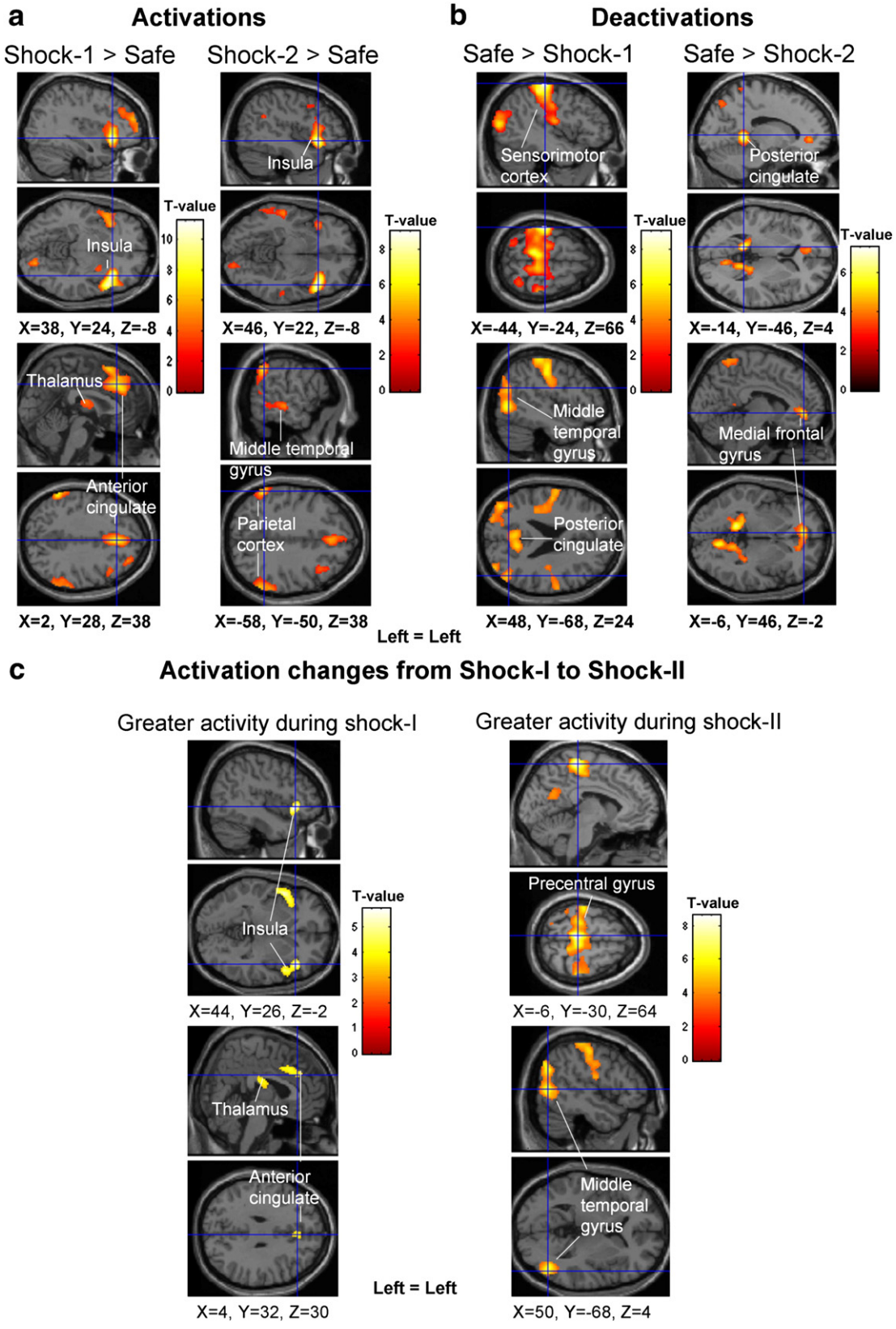

Fig. 1. Activation changes (height threshold $p = 0.001$; all displayed clusters $p < 0.05$ corrected) between shock-I (1a) and shock-II (1b) relative to the safe condition, and shock-I and shock-II (1c) (height threshold $p = 0.01$; all displayed clusters $p < 0.05$ corrected) in sagittal and axial views with associated MNI co-ordinates (x, y, z).

Table 3
Peaks and sub-peaks of regions showing significant group differences in activity modulation from safe/shock-I to shock-II (height threshold $p = 0.01$).

Brain region	Brodmann area	MNI coordinates			Voxel *T* value	Cluster size (voxels)	Cluster *p* corrected for multiple comparisons
		X	*Y*	*Z*			
Shock-II>Safe							
VSZ>HC							
Fusiform/inferior temporal gyrus	37	42	−52	−16	4.11	1168	0.031
Parahippocampal gyrus	28	28	−44	−6	3.84		
Fusiform gyrus	19/37	30	−58	−12	3.51		
Shock-II>Shock-I							
Violent>Non-violent groups							
Middle occipital gyrus	18/19	26	−74	18	4.39	3635	<0.001
	18	−20	−78	20	4.13		
Posterior cingulate	31	−20	−70	6	3.93		
VSZ>HC							
Lingual/posterior cingulate gyrus	18/31	24	−66	2	4.49	4527	<0.001
Parahippocampal gyrus	28	28	−58	−2	4.39		
Middle occipital gyrus	18/19	26	−74	20	4.27		
VSZ>SZ							
Medial prefrontal/cingulate gyrus	11	20	32	−14	4.38	2176	<0.001
	24/25	−6	24	−2	4.26		
	32	−16	26	−8	4.26		
Middle temporal gyrus	39	42	−60	16	4.27	4008	<0.001
	21	50	−12	−2	3.92		
Posterior cingulate/cuneus	19	26	−74	14	4.01		
Middle temporal gyrus	20	−44	−34	−14	3.92	1155	0.016
	21	−36	−26	−6	3.57		
Middle occipital gyrus	18	−28	−84	10	4.54	1256	0.01
	19	−32	−76	24	4.02		
	18	−20	−66	6	3.93		
VSZ>APD							
Thalamus	n/a	16	−10	8	5.41	3492	<0.001
Caudate nucleus	n/a	12	20	0	4.90		

MNI: Montreal Neurological Institute.

groups vs HC, each of the clinical group against each other]. Next we extracted subject-specific activation values (SSVs) from the peak activation voxel for each of the regions differentiating two/more groups and examined them for their possible relationships with fear and shock anticipation ratings using Pearson's correlations, and with violence ratings using Spearman rank order correlations. Group differences in the regions (peak voxel) differentiating SZ and VSZ groups were re-evaluated using analysis of co-variance after co-varying general psychopathology scores.

3. Results

3.1. Demographic and clinical measures

Table 1 presents demographic, clinical (including medication and symptoms if relevant) and behavioural characteristics of study groups. The ANOVA results for Group effect are also presented in Table 1.

The four study groups were matched in terms of current age and predicted intelligence and differed only in their defining characteristics. The VSZ and SZ groups were comparable on positive and negative symptoms but, unexpectedly, VSZ patients had lower general psychopathology ratings than SZ patients. We probed this effect further at individual PANSS item level and found that VSZ patients had lower ratings on general psychopathology items measuring depression, somatic concerns, anxiety, tension, preoccupation and active social avoidance than SZ patients (all p values <0.05; data not shown). We also examined the difference between the VSZ and SZ groups using the 5-factors PANSS (Lindenmayer et al., 1995). We found that the two groups had comparable ratings on positive, cognitive and excitement components but the SZ group had higher ratings on depression [$F = 9.17$, $df = 1,24$, $p = 0.005$; SZ mean (SD) = 10.15 (2.99), VSZ mean (SD) = 6.77 (2.52)] and negative symptoms components [$F = 5.19$, $df = 1,24$, $p = 0.032$ SZ mean (SD) = 18.54 (5.22), VSZ mean (SD) = 14.08 (4.75)].

As recorded during interviews and noted in case files, 2 SZ patients had a previous history of using cannabis and 1 of using cannabis and lysergic acid diethylamide (last use more than 10 years prior to study participation). Of 13 APD patients, 2 had a history of alcohol dependence, 1 of alcohol and cannabis dependence, 2 of alcohol dependence and polysubstance misuse, and 5 of alcohol as well as polysubstance misuse. Of 13 VSZ patients, 2 had a history of alcohol dependence, 1 of solvent misuse, 2 of cannabis dependence, 1 of alcohol as well as polysubstance misuse (cannabis, ecstacy, lysergic acid diethylamide, amphetamine), and 1 had a history of alcohol dependence and polysubstance misuse.

3.2. Behavioural measures

All groups were more fearful during the shock than the safe conditions (Condition: $F = 47.35$, $df = 1,49$, $p < 0.001$) (see Table 1). Although Group × Condition effects

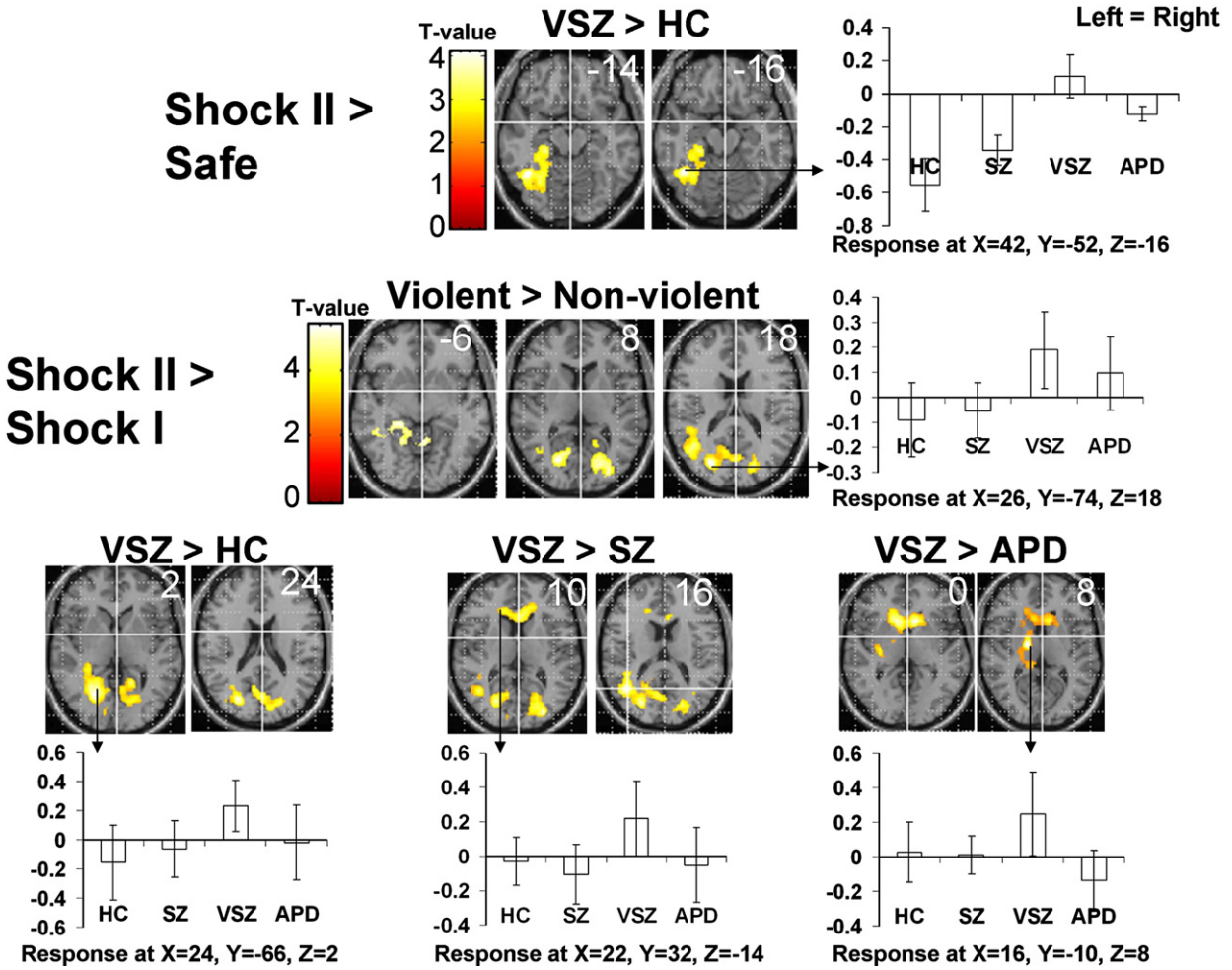

Fig. 2. Brain regions showing significant group differences in activity modulation from safe/shock-I to shock-II (height threshold $p = 0.01$; all displayed clusters $p < 0.05$ corrected) in axial views with associated MNI Z co-ordinates. Left hemisphere is shown on the right.

were non-significant ($ps > 0.10$), APD patients were generally the least, and VSZ patients generally the most, fearful of all groups, with a significant difference between these two groups over the safe and shock conditions ($p = 0.037$). For shock anticipation, there was a main effect of Group (see Table 1). APD patients had lower shock anticipation than HC ($p = 0.045$), SZ ($p = 0.01$) and VSZ patients ($p < 0.007$). VSZ patients reported the highest shock anticipation and differed, in addition to APD, from HC at a trend level ($p = 0.069$).

3.3. fMRI

3.3.1. Activation changes across all participants

3.3.1.1. Shock versus Safe. The insula, inferior frontal gyrus, AC and the inferior parietal cortex were activated during both shock-I and shock-II, relative to the safe condition (Table 2a, Fig. 1a). Additionally, there was activation in the thalamus and the striatum during shock-I, and in the left middle temporal lobe during shock-II, relative to the safe condition. There was reduced activity (deactivation) in the precentral, middle temporal, parahippocampal (extending to hippocampus) and posterior cingulate gyri during shock-I, and in the parahippocampal, medial frontal and precentral gyri, and precuneus during shock-II, both relative to the safe condition (Table 2b, Fig. 1b).

3.3.1.2. Shock-I versus shock-II. Activity declined significantly from shock-I to shock-II in the insula, AC, and thalamus (Table 2b, Fig. 1b). Activity increased (shock-II > shock-I) in the middle temporal, precentral and posterior cingulate gyri during shock-II relative to shock-I; these differences reflected a stronger deactivation of these regions during shock-I (than shock-II) rather than a stronger activation of these regions in shock-II (than shock-I) (Fig. 1a–c).

3.3.2. Group differences

3.3.2.1. Shock versus safe. All group differences presented in this section (also in Table 3 and Fig. 2) are derived from shock-I/ shock-II > safe contrasts (opposite patterns of group differences emerge for safe > shock-I/shock-II contrasts).

The ANOVA on shock-I > safe images revealed no group differences. The ANOVA on shock-II > safe images showed higher activity in the right inferior temporal, parahippocamal and fusiform gyri in VSZ patients compared with HC (Table 3, Fig. 2). These areas were part of the deactivation map for

shock-I (Fig. 1b) and were further deactivated to a variable degree during shock-II in all, but VSZ, groups. There was a positive association between fMRI response (SSVs at 42, −52, −16) and shock anticipation (entire sample: $r=-0.425$, $p=0.002$; VSZ alone: $r=-0.743$, $p=0.004$). No other group comparison revealed areas of significantly different activity.

3.3.2.2. Shock-I versus shock-II. Several group differences emerged in activity modulation from shock-I to shock-II. For clarity, all results as presented below (also in Table 3 and Fig. 2) are derived from shock-II>shock-I contrasts (opposite patterns emerge for shock-I>shock-II).

3.3.2.2.1. Violent versus non-violent groups. The violent groups (VSZ, APD), compared with the non-violent groups (SZ, HC), showed higher activity in the right middle occipital gyrus extending to the posterior cingulate and middle temporal gyri (Table 3, Fig. 2). These areas had shown deactivation during shock-I across all participants (Fig. 1b). Probing into this interaction revealed that these areas were further deactivated during shock-II in non-violent groups but returned to baseline (APD) or were somewhat activated (VSZ) in violent groups. There was no association between fMRI response (at 26, −74, 18) and fear or shock anticipation ratings, but it correlated positively with violence ratings ($rho=0.410$, $p=0.002$).

3.3.2.2.2. Individual group comparisons. VSZ patients, compared with HC, showed greater activity in a large right-sided cluster including parts of the posterior cingulate, parahippocampal, lingual and middle occipital gyri (Table 3, Fig. 2). These areas were deactivated during shock-I across all participants (Fig. 1b). The observed effect indicates that these were further deactivated during shock-II in HC but not in VSZ patients (Fig. 2).

VSZ, relative to SZ, patients showed greater activity in the left medial frontal/cingulate gyrus and bilaterally in the temporal-occipital regions. The differences resulted from deactivation of these areas during shock-II in SZ, but not in VSZ, patients. The differences in the left medial frontal cortex [ANOVA $F=17.86$, $df=1,24$, $p<0.001$; ANCOVA with general psychopathology score as a covariate, $F=14.60$, $df=1,23$, $p=0.001$), right temporal-occipital ($F=19.09$, $p<0.001$; ANCOVA $F=8.51$, $p=0.008$] and the left temporal regions ([$F=29.10$, $p<0.001$; ANCOVA $F=20.25$, $p<0.001$) remained significant after co-varying for general psychopathology scores. These areas had emerged as deactivations across all participants (Fig. 1b). The left medial frontal response was positively associated with shock anticipation across the whole sample ($rho=0.303$, $p=0.03$) and the left and right temporal–occipital responses with shock anticipation only in the VSZ group ($r=0.752$, $p=0.003$).

VSZ, relative to APD, patients showed higher activity in the right thalamus extending bilaterally to caudate nucleus (Table 3, Fig. 2). These areas were activated during shock-I, and more so than during shock-II, across all participants (Table 2a, Fig. 1b).

The observed effect indicated that thalamic-striatal activity increased in VSZ, but declined in APD, patients from shock-I to shock-II. SSVs in the thalamus were positively associated with fear ($r=0.301$, $p=0.028$) and shock anticipation ratings ($r=0.308$, $p=0.025$) across the entire sample.

Other group comparisons did not reveal areas of significantly different activity.

4. Discussion

To our knowledge this is the first study to examine the neural and behavioural responses to anticipatory fear in patients with schizophrenia, both with and without a history of seriously violent behaviour. In addition, we studied groups of non-violent HC and violent APD patients in order to elucidate behavioural and neural abnormalities associated specifically with a history of violence in schizophrenia.

4.1. Behavioural and clinical findings

Self-report data confirmed the effectiveness of our experimental manipulation in inducing anticipatory fear. Also confirming our expectations, our manipulation was the least effective in violent APD patients as they showed the lowest level of shock anticipation and fear. VSZ patients, on the other hand, showed the highest level of shock anticipation and fear of all groups. It is plausible that VSZ patients had higher positive symptoms at the time of offending, though not at the time of study participation, and a combination of positive symptomatic state, impaired frontal lobe function (Kumari et al., 2006), and heightened expectation of a negative outcome and fear when exposed to potential threat contributes to occurrence of repetitive and seriously violent behaviour in schizophrenia patients who do not have significant APD.

Another finding deserving some comment concerns unexpected lower general psychopathology scores, especially on depression, somatic concerns, anxiety, tension, preoccupation and active social avoidance items, in VSZ, relative to SZ, patients. As suggested earlier (Kumari et al., 2006), this finding may reflect the fact that VSZ patients had been living in secure hospitals whereas SZ patents were living in community and had to cope with social pressures and stigma associated with schizophrenia (Marie and Miles, 2008). Interestingly, a recent study has found a significantly lower incidence of criminal behaviour in schizophrenia patients with a depressive syndrome (Soyka et al., 2007), thus raising the possibility that the symptom profile of our non-violent schizophrenia group may reflect trait-like characteristics of patients who are less likely than normal for people with schizophrenia living in the community to engage in violent behaviour. The neural differences observed between SZ and VSZ patients, however, were not fully explained by differences in general symptom dimensions.

4.2. Activations/deactivations across all participants

The AC, medial/inferior frontal regions, insula, striatum and temporal regions were activated during anticipatory fear. These observations are consistent with previous relevant literature (e.g. Chua et al., 1999). The cingulate cortex and the insula serve to integrate the internal and external information (Mesulam and Mufson, 1982) and are found to be activated during emotional recall/imagery (review, Phan et al., 2002). The neural representation of fear is thought to be located within the AC/medial prefrontal cortex (review, Sewards and Sewards, 2003). The insula has established connections with the frontal, parietal and temporal lobes, cingulate gyrus, basal nuclei, amygdala and thalamus and serves (especially of the

anterior part) an important functional role in evaluating potentially distressing cognitive and sensory information (Reiman et al., 1989). Although basal ganglia structures have traditionally been linked to motor control and encoding of reward value, recent data implicate them in responses to stress and aversive stimuli (Schenberg et al., 2006; Scott et al., 2006). As discussed previously (Kumari et al., 2007), significant amygdala activity may not be observed, even during shock-I, with our experimental paradigm.

A number of regions were deactivated during shock-I and shock-II. Of these, activations of the medial frontal gyrus, parahippocampal gyrus/hippocampus, PC, precuneus and occipital regions are commonly seen during 'resting' states and viewed as the 'default' mode of brain function (Raichle and Snyder, 2007). The deactivation of the pre-/post central gyrus during shock-I may be associated with a sensory withdrawal/freezing in anticipation of an eminent electric shock after seeing the visual cue.

4.3. Neural effects associated with violence

The significant correlate of violence across the VSZ and APD groups consisted of altered activity modulation from shock-I to shock-II in occipital-temporal regions within the deactivation (default mode) network. The underlying mechanism for this effect, however, is very likely to be different in the VSZ and APD groups given observed differences (a) between these two groups in the levels of shock anticipation and fear, and (b) in activation patterns of VSZ and other study groups, particularly the APD group.

Specifically, VSZ patients showed some activation of the fusiform and parahippocamal gyri during shock-II (relative to safe) whereas HC (and other groups to some extent) showed deactivation. This effect strongly correlated with shock anticipation in VSZ patients and perhaps reflected their focus on the word 'shock' and the possibility of receiving shocks during the latter part of shock periods (Kuriki et al., 1998; Kiehl et al., 1999). Furthermore, the VSZ group showed increased whereas the APD group showed decreased thalamic-striatal activity during shock-II, relative to shock-I, periods. One possible explanation of this effect concerns the role of thalamus in arousal/attention (Van der Werf et al., 2002; Li and Kirouac, 2008) and the role of striatum in aversive conditioning (Menon et al., 2007). This in turn implies that VSZ patients, in association with a stronger conditioning, may have become more aroused by threat cues over a sustained period. Importantly, high arousal has been proposed to impede higher-level cognitive processing of attributions and therefore increase the likelihood of reactive (impulsive) kind of violence (Scarpa and Raine, 1997). In addition to the roles of thalamus and striatum in arousal/attention and aversive conditioning, these regions are also activated during voluntary or involuntary inhibition (Kumari et al., 2003; Ray Li et al., 2008). Enhanced thalamic-striatal activation in VSZ patients, thus, may also reflect an attempt (with or without success) on their part to inhibit an even greater belief/anticipation of receiving shocks during the latter part of shock periods (because none was received during shock-I). Activation, rather than deactivation, of default network indicates that they perhaps evoked self- (rather than situation-) focussed coping strategies as the threat condition progressed. APD patients who, on the other hand, feared and anticipated least the shocks, may have become even less attentive to the shock cues as the threat condition progressed, resulting in reduced thalamic-striatal activity and return to baseline activity in the default mode network.

Of the regions that showed altered activation patterns in the violent groups, temporal lobe regions have strongly been implicated in violent and antisocial behaviour (Dolan, 2002; Herba et al., 2004; Kumari and Taylor, in press). Abnormalities in the thalamus have been demonstrated in murderers (Raine et al., 1998), and in the basal ganglia in relation to aggressive behaviour in schizophrenia (Hoptman et al., 2006). How exactly these dysfunctions produce less/more favourable outcome in different violent scenarios in schizophrenia patients remains to be established. Our findings suggest their roles in enhanced neural and behavioural responses to perceived threat, if sustained over a period, in schizophrenia patients with a propensity to seriously violent behaviour.

4.4. Limitations

This study included patients with schizophrenia with various subtypes, symptoms and antipsychotic medications and patients with APD with other co-morbid personality disorders. Previous alcohol and substance misuse was present in some degree in all clinical groups but it was more common in the two violent groups. This is not surprising given a high level of substance abuse in both schizophrenia (Negrete, 2003) and APD (Lewis et al., 1893; Regier et al., 1990; Hatzitaskos et al., 1999) and that these populations are more likely to engage in violence in association with substance abuse (Miles et al., 2003). However, temporal lobe abnormalities are found in young subjects with early conduct disorder in absence of any substance misuse (Kruesi et al., 2004), thus our findings may not necessarily be affected by this possible confound.

5. Conclusions

This study demonstrated stronger aversive conditioning in men with schizophrenia and a history of violence than in men with APD and a similar violence history, with intermediate range for non-violent individuals (SZ men without a history of violence, healthy men), and aberrant activity modulation when exposed to threat cues over a sustained period in regions within the default node network in violent (VSZ, APD) compared to non-violent (SZ, HC) individuals, and opposite patterns of alternations in thalamic-striatal activity in VSZ (enhanced) and APD individuals (reduced). The common abnormality in the default mode regions in VSZ and APD most likely arises from dissimilar behavioural mechanisms, related to differences in the strength of aversive conditioning and processing of sustained threat cues, underscoring the need for differential strategies to manage violent behaviour in these two disorders.

Role of the funding source

The sponsors had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Contributors

Pamela Taylor and Veena Kumari contributed to funding acquisition. Veena Kumari, Mrigendra Das, Steven Williams and Christopher Andrew

contributed to the development of experimental paradigm and other imaging aspects. Pamela Taylor and Mrigendra Das contributed to clinical aspects. Mrigendra Das, Ian Barkataki and Alexander Sumich contributed to imaging and behavioural data acquisition. Veena Kumari, with advice from Dominic ffytche, analysed the data and prepared the first draft. All authors contributed to the final version.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

The study was supported by funds from the Zito Trust and the Community Fund, UK (RB218188) and the Stanley Medical Research Institute, USA (#098-208). VK is supported by the Wellcome Trust, UK (067427/z/02). We greatly appreciate Dr. Tonmoy Sharma's contribution to initial planning and multiple other aspects of this project and thank Ms. Lindsay Doswell for her assistance with processing of fMRI data.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.schres.2009.01.009.

References

Arseneault, L., Moffitt, T.E., Caps, A., Taylor, P.J., Silva, P.A., 2000. Mental disorders and violence in a total birth cohort. Arch. Gen. Psychiatry 57, 979–986.

Buchel, C., Morris, J., Dolan, R.J., Friston, K.J., 1998. Brain systems mediating aversive conditioning: an event-related fMRI study. Neuron 20 (5), 947–957.

Bright, P., Jaldow, E., Kopelman, M.D., 2002. The National Adult Reading Test as a measure of premorbid intelligence: a comparison with estimates derived from demographic variables. J. Int. Neuropsychol. Soc. 8 (6), 847–854.

Chua, P., Krams, M., Toni, I., Passingham, R., Dolan, R., 1999. A functional anatomy of anticipatory anxiety. Neuroimage 9, 563–571.

Davidson, R.J., Putnam, K.M., Larson, C.L., 2000. Dysregulation in the neural circuitry of emotion regulation—possible prelude to violence. Science 289, 591–594.

Dolan, M., 2002. What neuroimaging tells us about psychopathic disorders. Hosp. Med. 63, 337–340.

Dolan, M., Park, I., 2002. The neuropsychology of antisocial personality disorder. Psychol. Med. 32 (3), 417–427.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1995. Structured Clinical Interview for DSM-IV Axis I disorders, Patient Edition (SCID-P), version 2. New York State Psychiatric Institute, Biometrics Research, New York.

First, M.B., Gibbon, M., Spitzer, R.L., Williams, J.B., Benjamin, L.S., 1997. Users Guide for the Structured Clinical Interview for DSM IV Axis II Personality Disorders. New York State Psychiatric Institute, Biometrics Research, New York.

Fullam, R., Dolan, M., 2006. Emotional information processing in violent patients with schizophrenia: association with psychopathy and symptomatology. Psychiatry Res. 141 (1), 29–37.

Grillon, C., Ameli, R., Goddard, A., Woods, S.W., Davis, M., 1994. Baseline and fear-potentiated startle in panic disorder patients. Biol. Psychiatry 35 (7), 431–439.

Gunn, J., Robertson, G., 1976. Drawing a criminal profile. Br. J. Criminology 16, 156–160.

Gur, R.E., McGrath, C., Chan, R.M., Schroeder, L., Turner, T., Turetsky, B.I., Kohler, C., Alsop, D., Maldjian, J., Ragland, J.D., Gur, R.C., 2002. An fMRI study of facial emotion processing in patients with schizophrenia. Am. J. Psychiatry 159 (12), 1992–1999.

Hatzitaskos, P., Soldatos, C.R., Kokkevi, A., Stefanis, C.N., 1999. Substance abuse patterns and their association with psychopathology and type of hostility in male patients with borderline and antisocial personality disorder. Compr. Psychiatry 40 (4), 278–282.

Herba, C.M., Hodgins, S., Blackwood, N., Kumari, V., Naudts, K.H., Phillips, M.L., 2004. The Neurobiology of psychopathy: a focus on emotion processing. In: Herve, H., Yuille, J. (Eds.), Psychopathy: Theory, Research and Social Implications. Lawrence Erlbaum, Mahwah, New Jersey. 2006.

Herpertz, S.C., Sass, H., 2000. Emotional deficiency and psychopathy. Behav. Sci. Law 18 (5), 567–580.

Hodgins, S., 1992. Mental disorder, intellectual deficiency, and crime. Evidence from a birth cohort. Arch. Gen. Psychiatry 49, 476–483.

Hoptman, M.J., Volavka, J., Czobor, P., Gerig, G., Chakos, M., Blocher, J., Citrome, L.L., Sheitman, B., Lindenmayer, J.P., Lieberman, J.A., Bilder, R.M., 2006. Aggression and quantitative MRI measures of caudate in patients with chronic schizophrenia or schizoaffective disorder. J. Neuropsychiatry Clin. Neurosci. 18 (4), 509–515.

Kay, S.R., Fishbein, A., Olper, L.A., 1987. The positive and negative syndrome scale. Schizophr. Bull. 13, 261–276.

Kiehl, K.A., 2006. A cognitive neuroscience perspective on psychopathy: evidence for paralimbic system dysfunction. Psychiatry Res. 142 (2–3), 107–228.

Kiehl, K.A., Liddle, P.F., Smith, A.M., Mendrek, A., Forster, B.B., Hare, R.D., 1999. Neural pathways involved in the processing of concrete and abstract words. Hum. Brain Mapp. 7 (4), 225–233.

Krakowski, M., 2005. Schizophrenia with aggressive and violent behaviours. Psychiatr. Ann. 35, 45–49.

Kumari, V., Taylor, P., In press. Brain imaging studies as a route to understanding violent and criminal behaviour. In Gunn. J., Taylor. P., (Eds), Forensic Psychiatry. 2nd Edition. Hodder & Stoughton.

Kumari, V., Gray, J.A., Geyer, M.A., ffytche, D., Soni, W., Mitterschiffthaler, M.T., et al., 2003. Neural correlates of tactile prepulse inhibition: a functional MRI study in normal and schizophrenic subjects. Psychiatry Res. 122 (2), 99–113.

Kumari, V., Aasen, I., Taylor, P., ffytche, D.H., Das, M., Barkataki, I., Goswami, S., O'Connell, P., Howlett, M., Williams, S.C., Sharma, T., 2006. Neural dysfunction and violence in schizophrenia: an fMRI investigation. Schizophr. Res. 84 (1), 144–164.

Kumari, V., ffytche, D.H., Das, M., Wilson, G.D., Goswami, S., Sharma, T., 2007. Neuroticism and brain responses to anticipatory fear. Behav. Neurosci. 121 (4), 643–652.

Kuriki, S., Takeuchi, F., Hirata, Y., 1998. Neural processing of words in the human extrastriate visual cortex. Brain Res. Cogn. Brain Res. 6 (3), 193–203.

Kruesi, M.J., Casanova, M.F., Mannheim, G., Johnson-Bilder, A., 2004. Reduced temporal lobe volume in early onset conduct disorder. Psychiatry Res. 132 (1), 1–11.

Menon, M., Jensen, J., Vitcu, I., Graff-Guerrero, A., Crawley, A., Smith, M.A., Kapur, S., 2007. Temporal difference modeling of the blood-oxygen level dependent response during aversive conditioning in humans: effects of dopaminergic modulation. Biol. Psychiatry 62 (7), 765–772.

Mesulam, M.M., Mufson, E.J., 1982. Insula of the old world monkey. I Architectonics in the insulo-orbito-temporal component of the paralimbic brain. J. Comp. Neurol. 212, 1–22.

Li, S., Kirouac, G.J., 2008. Projections from the paraventricular nucleus of the thalamus to the forebrain, with special emphasis on the extended amygdala. J. Comp. Neurol. 506 (2), 263–287.

Lewis, C.E., Rice, J., Helzer, J.E., 1893. Diagnostic interactions. Alcoholism and antisocial personality. J. Nerv. Ment. Dis. 171 (2), 105–113.

Lindenmayer, J.P., Grochowski, S., Hyman, R.B., 1995. Five factor model of schizophrenia: replication across samples. Schizophr. Res. 14 (3), 229–234.

Marie, D., Miles, B., 2008. Social distance and perceived dangerousness across four diagnostic categories of mental disorder. Aust. N. Z. J. Psychiatry 42 (2), 126–133.

Miles, H., Johnson, S., Amponsah-Afuwape, S., Finch, E., Leese, M., Thornicroft, G., 2003. Characteristics of subgroups of individuals with psychotic illness and a comorbid substance use disorder. Psychiatr. Serv. 54 (4), 554–561.

Narayan, V.M., Narr, K.L., Kumari, V., Woods, R.P., Thompson, P.M., Toga, A.W., Sharma, T., 2007. Regional cortical thinning in subjects with violent antisocial personality disorder or schizophrenia. Am. J. Psychiatry 164 (9), 1418–1427.

Negrete, J.C., 2003. Clinical aspects of substance abuse in persons with schizophrenia. Can. J. Psychiatry 48 (1), 14–21.

Nelson, H.E., McKenna, P., 1975. The use of current reading ability in the assessment of dementia. Br. J. Soc. Clin. Psychol. 14, 259–267.

Nelson, H.E., O'Connell, A., 1978. Dementia: the estimation of premorbid intelligence levels using the New Adult Reading Test. Cortex 14, 234–244.

Nelson, H.E., Willison, J., 1991. National Adult Reading Test (NART) Test Manual, 2nd ed. NFER-Nelson, Windsor.

O'Carroll, R., Walker, M., Dunan, J., Murray, C., Blackwood, D., Ebmeier, K.P., Goodwin, G.M., 1992. Selecting controls for schizophrenia research studies: the use of the National Adult Reading Test (NART) is a measure of premorbid ability. Schizophr. Res. 8 (2), 137–141.

Ogawa, S., Lee, T.M., Kay, A.R., Tank, D.W., 1990. Brain magnetic resonance imaging with contrast dependent blood oxygenation. Proc. Nat. Acad. Sci. U. S. A. 87, 8868–8872.

Phan, K.L., Wager, T., Taylor, S.F., Liberzon, I., 2002. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. Neuroimage 16 (2), 331–348.

Raichle, M.E., Snyder, A.Z., 2007. A default mode of brain function: a brief history of an evolving idea. Neuroimage 37 (4), 1083–1090.

Raine, A., Meloy, J.R., Bihrle, S., Stoddard, J., LaCasse, L., Buchsbaum, M.S., 1998. Reduced prefrontal and increased subcortical brain functioning assessed using positron emission tomography in predatory and affective murderers. Behav. Sci. Law 16 (3), 319–332.

Ray Li, C.S., Yan, P., Sinha, R., Lee, T.W., 2008. Subcortical processes of motor response inhibition during a stop signal task. Neuroimage 41 (4), 1352–1363.
Regier, D.A., Farmer, M.E., Rae, D.S., Locke, B.Z., Keith, S.J., Judd, L.L., Goodwin, F.K., 1990. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. JAMA 264 (19), 2511–2518.
Reiman, E.M., Fusselman, M.J., Fox, P.T., Raichle, M.E., 1989. Neuroanatomical correlates of anticipatory anxiety. Science 243 (4894 Pt 1), 1071–1074.
Scarpa, A., Raine, A., 1997. Psychophysiology of anger and violent behavior. Psychiatr. Clin. North Am. 20 (2), 375–394.
Schenberg, E.E., Ferreira, T.L., Figueredo, L.Z., Hipolide, D.C., Nobrega, J.N., Oliveira, M.G., 2006. Fear conditioning performance and NMDA receptor subtypes: NR2A differential expression in the striatum. Brain Res. Bull. 69 (4), 440–446.
Scott, D.J., Heitzeg, M.M., Koeppe, R.A., Stohler, C.S., Zubieta, J.K., 2006. Variations in the human pain stress experience mediated by ventral and dorsal basal ganglia dopamine activity. J. Neurosci. 26 (42), 10789–10795.
Sewards, T.V., Sewards, M.A., 2003. Representations of motivational drives in mesial cortex, medial thalamus, hypothalamus and midbrain. Brain Res. Bull. 61 (1), 25–49.
Silver, H., Goodman, C., Knoll, G., Isakov, V., Modai, I., 2005. Schizophrenia patients with a history of severe violence differ from nonviolent schizophrenia patients in perception of emotions but not cognitive function. J. Clin. Psychiatry 66 (3), 300–308.
Soyka, M., Graz, C., Bottlender, R., Dirschedl, P., Schoech, H., 2007. Clinical correlates of later violence and criminal offences in schizophrenia. Schizophr. Res. 94 (1–3), 89–98.
Spitzer, R.L., Williams, J.B.W., Gibbon, M., First, M.B., 1990. Structured Clinical Interview for DSM-III-R Axis II Disorders (SCID-II). American Psychiatric Press Inc, Washington, DC.
Van der Werf, Y.D., Witter, M.P., Groenewegen, H.J., 2002. The intralaminar and midline nuclei of the thalamus. Anatomical and functional evidence for participation in processes of arousal and awareness. Brain Res. Brain Res. Rev. 39, 107–140.
Williams, L.M., Das, P., Harris, A.W., Liddell, B.B., Brammer, M.J., Olivieri, G., Skerrett, D., Phillips, M.L., David, A.S., Peduto, A., Gordon, E., 2004. Dysregulation of arousal and amygdala-prefrontal systems in paranoid schizophrenia. Am. J. Psychiatry 161 (3), 480–489.