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Neural Correlates of Psychopathic Traits in Schizophrenia: fMRI Study of Response Inhibition in Persistently Violent Patients

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***Background and Hypothesis*: Psychopathic traits play an important role in schizophrenia, particularly for violent behavior. There have been very few functional imaging studies (fMRI) examining the impact of brain dysfunction on psychopathic traits in schizophrenia. Our goal was to evaluate neural abnormalities underlying these traits through fMRI in violent subjects with schizophrenia (VS) and in 3 comparison groups: healthy controls (HC), nonviolent patients (NV), and nonpsychotic violent subjects (NPV). *Study Design*: fMRI imaging was used to measure blood-oxygen-level-dependent activation in 95 subjects while they performed a Go/NoGo task: 26 VS, 25 NPV, 26 HC, and 18 NVS. Psychopathy was evaluated through the 2 factors of the Psychopathy Checklist (PCL:SV). The subjects were also evaluated for psychiatric symptoms and for educational achievement. *Study Results*: Hypoactivation of brain areas involved in response inhibition was related to the severity of psychopathic traits in the violent patients with schizophrenia. These areas included frontal regions, cingulate cortex, insula, precuneus, and basal ganglia. This association was very strong for the first PCL:SV factor, the affective-interpersonal traits, and moderate for the second PCL:SV factor, the antisocial-impulsive traits. The latter traits were also linked to poor educational achievement. *Conclusions*: The 2 psychopathic factors have different antecedents and are dissociable at the neural level in schizophrenia. Brain dysfunction is more strongly associated with the affective-interpersonal traits while the antisocial traits are associated with various factors. This has important implications for the conceptualization and treatment of violence in patients with schizophrenia.**

Key words: aggression/response inhibition/frontal lobes/insula

Introduction

Psychopathic traits have been associated with violence in mental illness and in schizophrenia. In a large study of 939 patients discharged from acute psychiatric units which included a wide variety of diagnoses,[1] psychopathy, as measured by the Psychopathy Checklist:Screening Version (PCL:SV),[2] was the risk factor that most clearly differentiated high-risk from low-risk violence groups. The PCL-SV was also associated with violent recidivism in the community by discharged psychiatric patients.[3]

Psychopathic traits have also been associated with violence in patients with schizophrenia. Psychopathy, as measured by the Psychopathy Checklist-Revised was strongly associated with violent recidivism in male offenders with schizophrenia.[4] The level of psychopathy, as measured by the PCL-SV, correlated with level of violence in 100 hospitalized patients with schizophrenia.[5] In another study,[6] psychopathy scores were higher for violent patients with schizophrenia than for nonviolent patients. There was an increase in the prevalence of psychopathy in homicide offenders with schizophrenia compared with nonviolent individuals with schizophrenia.[7]

Psychopathy has typically been divided into 2 factors: the first represents primary or core psychopathy and involves interpersonal and affective aspects, such as coldness, lack of empathy, and callous manipulation. The second factor consists of antisocial and impulsive behaviors. It represents secondary psychopathy and overlaps with antisocial personality disorder.[8,9] Other factors may play a role in its emergence, such as educational achievement, as measured by reading achievement The latter has been shown to be strongly associated with antisocial traits and antisocial behavior.[10]

Lack of proper behavioral inhibition, ie, disinhibited behavior, is an important aspect of psychopathy and violent behavior.[11–13] Poor inhibition has been measured experimentally through response inhibition tasks, the most common being the Go No-Go task.[14] Participants are required to respond to one type of stimuli which are frequently presented (Go trials) and refrain from responding to another type of stimuli which are infrequent (No-Go trials). This entails an effortful inhibition of the routine response. There is reduced inhibitory control among persons with psychopathy as evidenced by their performance on this task. In 1 study,[11] 30 offenders with psychopathy were compared with 30 offenders with no psychopathy on the Go/NoGo task. The psychopathic offenders made significantly more errors of commission. A study in juvenile subjects with psychopathy reported similar results.[12] In another study,[13] subjects with high Psychopathy Checklist score had a high rate of commission errors on a visual Go/NoGo task. A meta-analytic investigation of response inhibition and psychopathy[15] reports that there is no indication that one PCL factor is more important than the other in this association between psychopathy and commission errors on response inhibition tasks.

Response inhibition processes engage multiple brain areas, which consists of several frontal regions, the cingulate cortex, insula, and basal ganglia.[16,17] Of the frontal regions, the inferior frontal gyrus is of particular importance.[16,18] Functional imaging has demonstrated primarily activation of the right inferior frontal (IFG) regions for the Go/No-Go task,[19–21] but the left IFG is also involved.[22]

The medial prefrontal regions, and particularly the medial orbitofrontal cortex (OFC), play a prominent role in behavioral inhibition,[19,23] as does the middle PFC and dorsolateral prefrontal cortex (DLPFC).[24] Imaging studies have shown heightened activation generated from the OFC distributed across both OFC and DLPFC, including the middle frontal gyrus.[25–29]

Other areas which are activated during response inhibition include temporal regions,[30] precuneus,[31] both anterior[32] and posterior cingulate[33,34] and the insula.[35] The insula, as the integral hub of the Salience Network, has an important role in tasks involving attending to and responding to unexpected but salient stimuli, such as the No-Go cues. It marks such stimuli for additional processing and initiates appropriate responses.[35–39]

Response inhibition depends upon the interaction of the frontal control system with the basal ganglia which form a fronto-basal-ganglia inhibition network.[28] Brain activation on the Go NoGo task was observed in the caudate, in addition to the DLPFC, IFC, and anterior cingulate.[31] Basal ganglia lesions interfere with response inhibition.[40]

Many of the brain areas mentioned above, including OFC, medial prefrontal cortex, cingulate and precuneus, fusiform gyrus, insula and posterior temporal cortex, are involved in various aspects of social behavior, including social cognition, empathy, and the ability to make inferences about others' mental states, ie, theory of mind capacity.[41,42] Increased activation with mental state attribution has been reported in the fusiform gyrus, medial prefrontal, inferior frontal, orbitofrontal, and temporal cortices.[43,44]

A network mediating empathic responses include prefrontal structures and in particular the OFC.[45] The insula is also part of this network and is activated in empathic responses.[46–48]

These brain areas are impaired in persons with psychopathy. Cortical thinning has been reported in the left insula, left and right anterior temporal cortices, right inferior frontal gyrus and cingulate cortex in persons with psychopathy.[49,50] Similarly, fMRI studies of subjects with psychopathy indicate abnormalities in the temporal gyrus, cingulate cortex, and insula.[51] Furthermore, neural processes involved in response inhibition are abnormal in persons with psychopathy. One study[52] investigated whether subjects with psychopathy exhibited abnormal neural processing when suppressing inappropriate responses on the Go NoGo task. They produced abnormal neural responses to NoGo stimuli in the frontocentral areas with respect to event related potential (ERP) Negativity and failed to manifest the usual larger P375 component on NoGo trials. This was interpreted as indicative of abnormal neural processes in response inhibition in psychopathy. Another study used event-related fMRI to examine neurobiological correlates of response inhibition on a Go/NoGo task.[53] Persons with psychopathy showed less activation in lateral frontal cortex, bilaterally, than healthy controls during the NoGo trials. In the study mentioned above,[13] the patients with comorbid psychopathy showed a significantly reduced amplitude of an early frontal negative ERP component while performing a Go/NoGo task.

There are few fMRI studies that examine neurophysiological dysfunction linked to psychopathic traits in schizophrenia. This article investigates brain activation correlates of the 2 PCL-SV factors in violent patients with schizophrenia (VS). Our primary hypothesis is that in the VS group, the first PCL-SV factor is strongly related to decreased brain activation in brain areas involved in response inhibition. We hypothesize that the second PCL-SV factor is also related to decreased activation in these brain areas but not as strongly as the first, as additional influences come into play. In a secondary hypothesis, we posited a relationship between educational background, as measured by reading ability, on the PCL-SV. Thus, we hypothesized that greater deficit in reading ability is associated with higher scores on the PCL-SV second factor, in line with the literature reported above.[10]

Because violent patients with schizophrenia may share characteristics with nonpsychotic violent subjects and with nonviolent patients with schizophrenia, we focused on the neural mechanisms in these groups. This allows us

to disentangle the effects related to schizophrenia from those related to violence.

Methods

Study Design and Participants

Ninety-five subjects were included in our study: 26 violent patients (VS), 18 nonviolent patients (NV), 25 nonpsychotic violent subjects (NPV), and 26 healthy controls (HC). There were more patients initially, but some were excluded (see supplementary methodology). For inclusion as violent (VS or NPV), the participant was required to have at least one confirmed episode of physical assault in the past year, and at least one prior to this; they had to have a Life History of Aggression (LHA) score of ≥20. For inclusion as a nonviolent participant (HC or NV), the subject was required to have an LHA score ≤15 and no episode of physical aggression over the past year, or any lifetime episode of severe physical aggression. Additional requirements for violence and nonviolence are described in supplementary methodology.

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) was administered to confirm diagnosis of schizophrenia in the patients (Patient Version) and the absence of any psychotic disorder in the non-patient groups (Non-Patient Version). History of alcohol/drug abuse and dependence was also obtained as part of this diagnostic assessment. Participants who presented with drug or alcohol abuse in the preceding 6 months were excluded from the study, so that the results would not be confounded by this factor. We also obtained urine toxicology to exclude any patient with a positive urine screen. The subjects had no significant medical or neurological illness, including any history of seizure disorder or traumatic brain injury. All participants provided written informed consent according to a protocol approved by the institutional review boards and compliant with the Declaration of Helsinki.

Procedures

Response Inhibition Task Subjects completed a Go/No-Go inhibition task that presented a series of pictures from the International Affective Picture Set (IAPS).[54] All stimuli subtended 8.6 × 6.5°C of visual angle and were presented every 1000 ms. Each picture was presented for 800 ms, with a black screen presented during the interval between successive stimuli (for 200 ms). Participants were instructed to press a button when each stimulus was presented (Go trials). They were further instructed to withhold a response when any picture was repeated right after the previous picture which was the cue to withhold response (No-Go trials). In each of the 4 blocks, there were 180, 42 of which were No-Go (ie, repetition) trials (30.43%). IAPS pictures can have a neutral, positive, or negative emotional valence. There were twice as many images with neutral valence as compared with either positive or negative valences. As mentioned above, we included only participants who performed above 20% on the No-Go stimuli; this limited the statistical power for valenced stimuli. For these reasons we conducted the inferential statistical analyses for the group comparisons by using the neutral images. This allowed us to reduce heterogeneity and to investigate the basic response inhibition processes. The neutral pictures depicted people, landscapes, abstract patterns, and objects. The average valence for the neutral pictures was 5.2 and the arousal 3.5.

MRI scans were performed on a 1.5T Siemens Vision system (Erlangen, Germany) at the Center for Biomedical Imaging and Neuromodulation (CBIN) at the Nathan Kline Institute.

For the response inhibition task, 4 runs of functional scans were acquired (each of 105 volumes). For all runs, a T2-weighted echo-planar sequence was used (TR/TE = 2000/50 ms, flip angle = 85°, 5 mm slice thickness, 224 mm FOV, 64 × 64 matrix, pixel size = 3.5 × 3.5 mm, no gap). Twenty-two axial slices were obtained parallel to the anterior commissure-posterior commissure line. Structural images were acquired utilizing a T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) (TR/TE = 11.6/4.9 ms, flip angle = 8°, 172 slices, 1.20 mm slice thickness, 307 mm FOV, 256 × 256 matrix, pixel size = 1.20 × 1.20 mm, no gap).

The Image Processing of the data is described in supplementary methodology.

Assessments

The Psychopathy Checklist: Screening Version (PCL:SV) Specially trained Ph.D. psychologists conducted in-depth semi-structured interviews and reviewed all available records to complete the scale, which includes 2 factors: PCL:SV Factor 1, the Affective-Interpersonal and PCL:SV Factor 2, the Antisocial-Impulsive.[55] The Affective-Interpersonal factor is more specific to the psychopathy construct; the Antisocial-Impulsive factor overlaps with antisocial personality disorder.[8]

Assessment of Aggression

Life History of Aggression The LHA with well-established psychometric properties[56] was one of the measures used to assess aggression. It was completed based on all available information, including self-report, chart review, and official records of arrests, convictions, parole, and probation obtained from the Division of Criminal Justice Services.

Modified Overt Aggression Scale

The "Physical Aggression Against Other People" subscale of the Modified Overt Aggression Scale (MOAS) was used to rate the recorded incidents of physical aggression.[57] Severity on this subscale varies from mild to severe.

The interrater reliability, estimated by intraclass correlation coefficient, was established prior to the study. It was above 0.90.

The Positive and Negative Syndrome Scale

The Positive and Negative Syndrome Scale (PANSS) was used to assess psychiatric symptoms in the 2 patient groups. Interrater reliability, estimated by intraclass correlation coefficient, exceeded 0.90.[58]

The Wide Range Achievement Test—Third Edition, Reading Subtest

The Wide Range Achievement Test—Third Edition, Reading Subtest (WRAT-3) is a well-accepted method of estimating educational achievement, including premorbid academic skills and IQ.[59,60]

We were interested in the relationship between the WRAT-3 and the PCL-SV antisocial factor for the reasons mentioned above.

Statistical Methods

We used General Linear Modeling (GLM) to assess the relationship between brain activation and psychopathic traits. The dependent variable was the PCL-SV score for each factor separately. The main independent variable of interest was activation in specific brain areas. A separate analysis was conducted for each brain area. "Group" (ie, the 4 study groups, VS, NPV, HC, and NV) was another independent variable. The interaction between these 2 variables was also included.

We calculated the Least Square (LS) Means of the PCL:SV first and second factors when fMRI BOLD activation is 1 SD unit higher than the mean and when it is 1 SD unit lower than the mean. Age, gender as well as drug/alcohol abuse served as fixed-effect covariates in these analyses. We corrected the results for multiple testing by applying the False Discovery Rates correction.[61]

In these analyses, we investigated the hypothesis that when brain activation is low, the PCL-SV first factor severity in VSs would be significantly higher than in HCs who do not have psychopathic traits; it would be similar to the NPVs who are strongly psychopathic. When brain activation is high, on the other hand, we hypothesized that the PCL-SV first factor severity in the VSs would be significantly lower than that of the NPVs and similar to the HCs. A similar pattern would also be present for the second PCL-SV factor but in a more limited way.

Results

Demographic and Clinical Variables

Table 1 displays the demographic and clinical information for the 4 study groups. Overall and pairwise comparisons are provided. There were no significant differences among the groups in gender or ethnicity, but there was a significant difference in years of education. The 2 violent groups, NPV and VS, had significantly greater frequencies of alcohol and drug abuse/dependence than the nonviolent groups, HC and NV. Diagnostic information was also obtained in the nonpsychotic patients. In HC, 1 subject had a history of major depressive disorder. In NPV, 6 subjects had a history of major depressive disorder and 1 of anxiety disorder.

Significant differences in physical aggression, as measured by LHA Physical aggression, between the violent and nonviolent groups were obtained, as expected, as this was a criterion for group formation. NPVs presented with severe psychopathic traits and had significantly higher scores than the other 3 groups, including VSs, on the 2 PCL-SV factors The VSs had higher PCL-SV factor scores than the nonviolent groups. The PANSS Total score was similar in the 2 groups with schizophrenia.

On the Go/NoGo Task, there were significant overall group differences in commission errors ($F = 14.9$, df = 2,92, $P < .001$). Both patient groups made significantly more commission errors than HCs and NPVs ($P < .01$ for all pairwise comparisons). NPVs made more commission errors than HCs ($P = .02$). The VS-NV difference, however, was not significant ($P > .1$).

Activation patterns across the 4 groups are shown in figures 1 and 2. Numerous regions emerged as showing significant differences from null activation, most of which are involved in response inhibition and/or emotional processing. These are shown in supplementary table 1.

There were no significant differences in brain activation among the 4 groups in the selected brain areas.

Neural Correlates of Affective-Interpersonal Psychopathy Traits in Violent Patients With Schizophrenia as Compared With the Other Groups Table 2 presents the neural correlates of PCL-SV Factor 1, the Affective-Interpersonal factor. We are presenting the LS Means of this factor for each group when there is lower activation and when there is higher activation in the brain areas of interest. We are also presenting the overall interaction effect between group and brain activation in determining the first factor score. Finally, we provide *P* values for the pairwise differences between VSs and each of the comparison groups, NPVs, NVs, and HCs, first when there is low brain activation and then when there is high brain activation.

As can be seen from table 2, NPVs have uniformly high scores on the first PCL:SV factor while the 2 nonviolent groups have consistently low scores, regardless of brain activation level. In VSs, on the other hand, the scores differ greatly as a function of brain activation. With lower activation, the scores are high in all brain areas of interest and very similar to the NPVs. These scores are markedly higher ($P < .001$) than those for the nonviolent groups.

Table 1. Demographic and Clinical Characteristics of Healthy Controls (HC), Nonpsychotic Violent Subjects (NPV), Nonviolent (NV), and Violent (VS) Patients With Schizophrenia[a]

Characteristics	HC, $N = 26$	NPV, $N = 25$	NV, $N = 18$	VS, $N = 26$	χ^2, P
Male, N (%)	17 (65.4)	24 (96.0)	14 (77.8)	20 (76.9)	7.33, .06
Race/ethnicity, N (%)					
Caucasian	12 (46.2)	8 (32.0)	6 (33.3)	6 (23.1)	
African American	14 (53.9)	17 (68.0)	12 (66.7)	20 (76.9)	3.15, .37
Subjects with any drug or alcohol abuse/dependence[b], N (%)	2 (7.7)	18 (72)	3 (16.7)	16 (61.5)	30.8, <.001
					F, P
Mean age, in years	38.5 (10.5)	38.1 (10.3)	40.6 (8.8)	36.7 (11.0)	0.53, .66
Years of education[c]	14.4 (1.8)	12.3 (1.8)	12.5 (1.0)	12.0 (1.9)	10.1, <.001
Age at first hospitalization	—	—	22.9 (6.2)	23.5 (9.9)	0.04, .84
Percent false alarms[d]	30.6 (15.5)	41.1 (18.0)	56.5 (15.7)	55.9 (16.0)	13.04, <.001
Reaction time for false alarms[e]	357.0 (121.6)	338.8 (61.2)	424.1 (55.0)	383.8 (85.7)	3.812, .01
WRAT-3[f] scores	51.0 (8.5)	45.1 (8.9)	38.9 (9.4)	46.4 (7.5)	7.0, <.001
PANSS[g] Total score	—	—	75.3 (13.8)	74.8 (14.9)	.01, .91
LHA Total Aggression score[h]	13.7 (7.0)	34.7 (8.2)	11.4 (7.2)	23.6 (5.9)	62.1, <.001
LHA Physical Aggression[i]	1.3 (1.5)	4.2 (1.5)	1.2 (1.0)	3.5 (1.1)	25.2, <.001
PCL-SV Factor 1[j]	1.24 (1.85)	9.08 (1.41)	2.16 (1.85)	6.05 (3.32)	60.1, <.001
PCL-SV Factor 2[j]	1.52 (1.56)	9.84 (1.18)	2.16 (2.04)	6.62 (3.31)	75.8, <.001
Antipsychotic dosage (chlorpromazine equivalents)	—	—	1103.2 (660.4)	1245.5 (649.6)	0.71, .40

[a]For categorical variables data are presented as relative frequencies; for continuous variables means and SDs are provided.
[b]Subjects with abuse/dependence within 6 months prior to evaluation were not enrolled in the study. Overall chi-square is reported for alcohol/substance abuse or dependence in the 4 groups. The frequency of alcohol use or abuse and drug use or abuse is significantly higher in NPVs than in HCs and NVs ($P < .001$) but does not differ from VSs; the frequency in VSs is higher than in HCs ($P = .001$) and NVs ($P = .006$).
[c]The number of years of education is higher in the HC than in each of the other 3 groups ($P < .001$). There are no other pairwise differences.
[d]In pairwise comparisons, the HCs have fewer false alarms than the NPVs ($P = .04$) and the 2 patient groups ($P < .001$); the NPVs have fewer false alarms than the NVs and VSs ($P < .01$).
[e]In pairwise comparisons, HCs respond significantly faster than NVs ($P < .01$) and marginally faster than VSs ($P = .07$). NPVs respond faster than NVs ($P < .01$) and VSs ($P = .04$).
[f]Wide Range Achievement Test (third edition) Reading Subtest. HCs have significantly better scores than NPVs ($P = .02$) and NVs ($P < .001$) and a marginally better score than VSs ($P = .06$). NVs have poorer scores than NPVs ($P = .02$) and VSs ($P < .01$).
[g]The Positive and Negative Syndrome Scale.
[h]In pairwise comparisons for the Life History of Aggression (LHA) total Aggression, NPVs have significantly higher score than the other 3 groups ($P < .001$). VS has a higher score than NVs and HCs ($P < .001$).
[i]This is based on the score on the LHA item "Specific assaults on other people." In pairwise comparisons for the LHA Physical Aggression item, NPVs have significantly higher score than each of the 2 nonviolent groups ($P < .001$) and a marginally higher score than VS ($P = .08$). VSs have a higher score than NVs and HCs ($P < .001$).
[j]In pairwise comparisons for both the Psychopathy Checklist: Screening Version (PCL-SV) first and second factors, NPVs have a higher score than all 3 groups including VSs ($P < .001$); VSs have a higher score than HCs and NVs ($P < .001$ for each); there is no difference between HCs and NVs.

With higher brain activation, the opposite is true: The VS's scores on the first factor are similar to the HC's and NV's and significantly lower than NPVs in all brain areas of interest ($P < .001$), except for the left middle frontal gyrus and right inferior temporal gyrus.

We chose 1 brain area to illustrate visually these PLC-SV differences among the 4 groups (see supplementary figure 1).

Neural Correlates of Antisocial Psychopathic Traits in Violent Patients With Schizophrenia as Compared With the Other Groups Table 3 presents the neural correlates of the second PCL-SV factor, the antisocial traits (supplementary figure 1). The brain areas presented in the table are those in which there was a significant interaction between grouping and brain activation in determining the second PCL:SV factor score. The results are presented in the same way as those for the first PCL:SV factor in table 2.

With low activation of the brain areas, VS's scores are similar to NPV's. With high activation, however, we obtain different results than for the first factor. While the severity of antisocial traits diminishes with increased brain activation, this decrease is not as pronounced as was the case for first factor and the scores remains in the mid-range; they are significantly lower than NPVs but still higher than HCs and NVs, as shown in the table.

This pattern of differences among the 4 groups is visually illustrated in 1 brain area in supplementary figure 1.

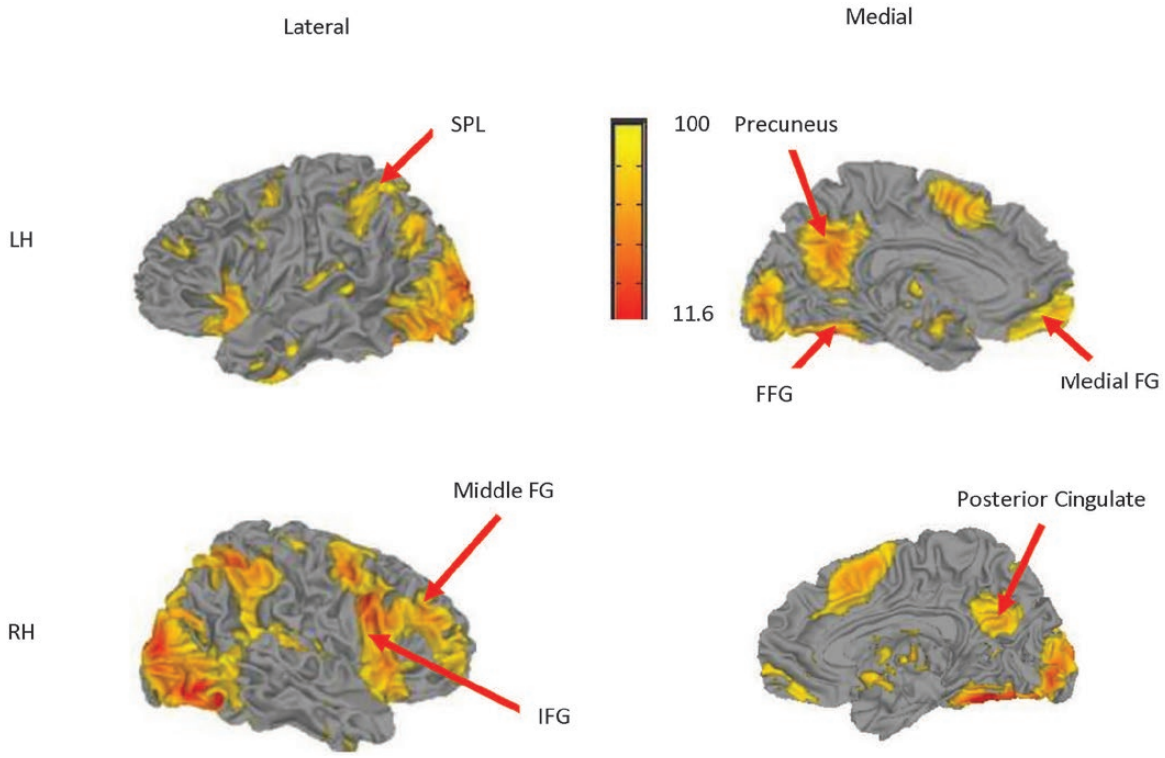

Fig. 1. Activation for intercept of GLM on No-Go trials. Displayed are left lateral and medial surfaces (top row) and right lateral and medial cortical surfaces (bottom row). Flame scale shows *F* values (11.6–100). Arrows point to significant peak regions: FFG, fusiform gyrus; IFG, inferior frontal gyrus; Middle FG, middle frontal gyrus; SPL, superior parietal lobule.

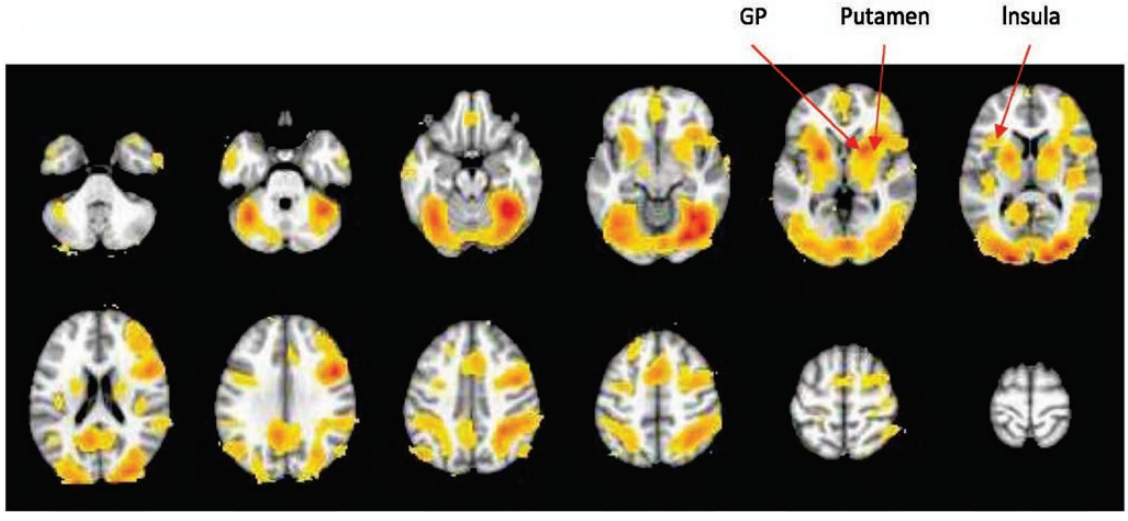

Fig. 2. Task-related activation superimposed on axial slices of the anatomical template. Every fifth slice is shown. Arrows point to insula, putamen, and globus pallidus (GP). Flame scale is as in the figure.

In NPVs, brain activation is not associated with PCL-SV score for Factor 1 or 2. The PCL-SV scores are high whether brain activation is high or low. Variation in PCL-SV scores in this group is limited, as all subjects have severe psychopathic traits.

Association Between Reading Ability and the Two PCL-SV Factors We looked at the relationship between the WRAT-3 and the 2 PCL-SV factors. There was a significant correlation with the second factor ($r = -0.46$, $N = 24$, $P = .03$) but not with the first ($r = -0.18$). Thus,

Table 2. Scores on the First PCL:SV Factor for the 4 Groups of Subjects, Violent Patients With Schizophrenia, Nonpsychotic Violent Subjects, Healthy Controls, and Nonviolent Patients With Schizophrenia When There Is Low and High Brain Activation in the Selected Brain Areas[a]

		VS Group PCL 1st Factor LS Mean[a]		NPV Group PCL 1st Factor LS Mean		HC Group PCL 1st Factor LS Mean		NV Group PCL 1st Factor LS Mean		Interaction Among the Groups	Pairwise Differences in PCL-SV Score When There Is Low Activation. VS Compared With:			Pairwise Differences in PCL-SV Score When There Is High Activation. VS Compared With:		
Brain Area		Low Act.	High Act.	Low Act.	High Act.	Low Act.	High Act.	Low Act.	High Act.	*F*, *P*	NPV Low Act.	HC Low Act.	NV Low Act.	NPV High Act	HC High Act	NV ~~High~~ Act
IFG	R	8.37	2.70	8.45	9.80	0.87	1.96	1.94	2.49	3.86, .01	.94	<.001	<.001	<.001	.67	.92
	L	8.16	2.96	8.51	9.63	1.06	1.53	1.93	2.43	3.18, .03	.75	<.001	<.001	<.001	.40	.76
Medial FG	R	9.76	3.47	9.20	8.95	0.66	2.04	2.40	3.47	5.57, .002	.63	<.001	<.001	<.001	.28	.20
	L	9.67	3.48	9.24	8.89	0.77	1.91	2.41	2.01	5.33, .002	.70	<.001	<.001	<.001	.24	.19
Middle FG	R	8.88	3.82	8.54	9.62	2.29	0.48	2.05	2.27	2.39, .07	.81	.002	<.001	<.001	.04	.34
	L	7.79	4.63	9.14	9.03	1.66	0.88	2.09	2.25	0.55, NS	.37	<.001	.02	<.001	.01	.31
Inferior TG	R	7.29	4.81	8.89	9.20	1.62	0.95	2.20	2.14	0.73, NS	.21	<.001	.01	<.001	.005	.08
	L	8.14	3.39	9.24	8.94	0.63	1.98	2.54	1.99	2.51, .06	.35	<.001	<.001	<.001	.36	.28
Fusiform gyrus	R	8.63	3.89	8.34	9.67	–0.35	3.17	1.53	2.72	4.79, .004	.81	<.001	.002	<.001	.65	.54
	L	8.48	4.13	8.32	9.64	−0.32	2.96	1.71	2.53	4.58, .005	.89	<.001	<.001	<.001	.43	.35
Insula	R	8.17	3.73	8.75	9.53	0.42	2.61	3.00	1.46	2.37, .07	.64	<.001	.009	<.001	.53	.21
	L	8.26	3.86	8.73	9.45	0.51	2.28	2.40	1.99	2.41, .07	.70	<.001	.001	<.001	.31	.22
Cingulate	R	8.51	3.74	8.79	9.36	0.99	1.53	3.02	1.60	2.86, .04	.82	<.001	<.001	<.001	.10	.12
	L	8.27	3.77	8.86	9.32	0.87	1.70	2.75	1.78	2.68, .05	.61	<.001	<.001	<.001	.13	.14
Basal ganglia	R	7.81	3.42	8.53	9.52	0.56	2.20	2.56	1.64	3.49, .02	.49	<.001	<.001	<.001	.41	.34
	L	7.59	3.17	8.49	9.65	0.99	1.66	1.86	2.60	3.02, .03	.39	<.001	<.001	<.001	.37	.75
Precuneus	R	8.72	3.19	8.46	9.69	0.25	2.62	2.01	2.31	4.78, .004	.83	<.001	<.001	<.001	.71	.61
	L	7.77	3.75	8.28	10.10	0.42	2.67	2.51	1.69	2.92, .04	.65	<.001	.002	<.001	.54	.33

Act., activation; FG, frontal gyrus; HC, healthy controls; IFG, inferior frontal gyrus; NPV, nonpsychotic violent subjects; NV, nonviolent patients with schizophrenia; TG, temporal gyrus; VS, violent patients with schizophrenia.

[a]The table presents the Least Square (LS) Means for the first PCL-SV factor for each of the 4 study groups.

The LS Means are provided for low and high activation, defined as 1 SD below the mean and 1 SD above the mean, respectively. This is equivalent to 1 in terms of standardized *z* score unit. We thereby provide predicted PCL-SV values for a high value and a low value of brain activation, respectively. This method does not reduce the number of participants, as it uses the data from the entire study population for prediction.

The *F* and *P* values for the interaction between brain activation and grouping are also presented in the table. The last sets of columns in the table present the *P* values for the pairwise comparisons between the VS group and each of the 3 comparison groups, the NPV, HC, and NV. We present these pairwise differences between the groups first when there is low brain activation and then when there is high activation in each of the brain areas. For low brain activation, we were primarily interested in the pairwise differences between the VS and HC (and NVS), as we hypothesized that the PCL-SV first factor score would be significantly higher in the VS group (as explained in the text).

For high brain activation, we were primarily interested in the pairwise differences between the VS and NPV, as we hypothesized that the PCL-SV first factor score would be significantly lower in the VS group. We applied the False Discovery Rate (FDR) approach for multiple testing correction in order to control for alpha inflation in pairwise comparisons. All results for the pairwise comparisons that are nominally significant at low activation remained significant after correction. For high activation the differences between the VS and NPV remained significant after correction. In the comparisons with HC and NVS group only 1 comparison remained significant (right inferior temporal gyrus).

Table 3. Scores on the Second PCL:SV Factor for the 4 Groups of Subjects, the Violent Patients With Schizophrenia (VS), the Nonpsychotic Violent Subjects (NPV), the Healthy Controls (HC), and the Nonviolent Patients With Schizophrenia (NV) When There Is Low and High Brain[a] Activation in the Selected Brain Areas[a]

		VS Group PCL 2nd Factor LS Mean[b]		NPV Group PCL 2nd Factor LS Mean		HC Group PCL 2nd Factor LS Mean		NV Group PCL 2nd Factor LS Mean		Interaction Effect[b]	Pairwise Differences in PCL-SV Score When There Is Low Activation. VS Compared With:			Pairwise Differences in PCL-SV Score When There Is High Activation. VS Compared With:		
Brain Area		Low Act.	High Act.	Low Act.	High Act.	Low Act.	High Act.	Low Act.	High Act.	*F*, *P*	NPV Low Act.	HC Low Act.	NV Low Act.	NPV High Act	HC High Act	NV ~~High~~ Act
Medial FG	R	9.44	4.27	9.90	8.79	1.69	0.84	1.71	1.68	2.75, <.05	.70	<.001	<.001	<.001	.01	.03
	L	9.48	4.17	9.80	8.79	1.66	0.84	1.78	1.60	2.94, .04	.77	<.001	<.001	<.001	.01	.02
Middle FG	R	8.57	4.74	9.31	9.63	2.13	0.83	0.70	2.78	1.58, NS	.60	<.001	<.001	<.001	.02	.22
	L	9.41	3.99	8.83	9.94	0.81	1.84	0.34	3.22	3.26, .03	.68	<.001	<.001	<.001	.12	.73
Inferior TG	R	6.78	5.99	9.31	9.48	1.53	1.22	1.53	1.94	0.10, NS	.05	.002	.009	.002	.001	.008
	L	7.91	4.36	8.69	9.95	1.88	0.66	1.95	1.63	2.16, <.10	.49	<.001	<.001	<.001	.02	.04

Act., activation; FG, frontal gyrus; TG, temporal gyrus.

[a]The table presents the Least Square (LS) Means for the second PCL:SV factor for each of the 4 groups. The LS Means are provided for low and high activation, defined as 1 SD below and 1 SD above the mean, respectively. The *F* and *P* values for the interaction among the 4 groups are also presented. In the last sets of columns, the *P* values for the pairwise comparisons between the VS group and each of the 3 comparison groups, the NPV, HC, and NV, are presented, first for low brain activation and then for high brain activation. For low brain activation, we were primarily interested in the pairwise differences between the VS and HC, as we hypothesized that the PCL-SV second factor score would be significantly higher in the VS group (as explained in the text). For high brain activation, we were primarily interested in the pairwise differences between the VS and NPV groups, as we hypothesized that the PCL-SV second factor score would be significantly lower in the VS group. We applied False Discovery Rate approach for multiple testing correction in order to control for alpha inflation in pairwise comparisons. All results for the pairwise comparisons that are nominally significant at low activation remained significant after correction. For high activation the differences between the VS and NPV remained significant after correction. In the comparisons with HC and NVS group only 1 comparison remained significant (right inferior temporal gyrus).

[b]The *P* values for the interaction effect of group with brain activation are provided for significant and marginal results.

poorer educational achievement, as evidenced by reading ability, is associated with more severe antisocial traits.

Discussion

Brain Activation and Psychopathic Traits

The present study investigated associations between brain activation and psychopathic traits in violent patients with schizophrenia as contrasted to 3 comparison groups. We found that lower cerebral activation during a response inhibition task is associated with more severe psychopathic traits. The affective and interpersonal symptoms of psychopathy are strongly influenced by dysfunction in several brain areas which underlie response inhibition and various aspects of social functioning.

Our results indicate that low brain activation and the disease, ie, schizophrenia, jointly contribute to the outcome of interest which is the severity of psychopathic traits. Lower brain activation may be an important determinant of psychopathy in patients with schizophrenia who exhibit violent tendencies.

With lower activation of these brain areas, the affective-interpersonal traits were severe and similar to those of the nonpsychotic violent subjects, who evidence consistently high psychopathic traits. With high brain activation of these areas, on the other hand, the scores in the violent patients were low and comparable to those of the nonviolent groups who present with consistently low psychopathic traits.

In contrast, the antisocial traits are only moderately influenced by brain activation and fewer brain areas are involved. They consist of the medial and middle frontal gyrus, and the inferior temporal gyrus. The medial PFC, and particularly the OFC, as mentioned above, play a prominent role in response inhibition and social behavior. There are strong overall similarities in the social behaviors of subjects with OFC lesions and those with psychopathy and antisocial personality. For example, theory of mind impairment in psychopathy resembles impairment seen in subjects with OFC damage.[62] As mentioned above, the middle PFC and DLPFC are strongly associated with impairments in response inhibition and social functioning. Deficits in the temporal areas result in poor inhibition and lack of control over aggressive and antisocial behaviors.[63]

Fewer brain areas are involved and even in these areas, brain activation does not have as strong an impact on antisocial traits, as it does on affective-interpersonal traits. With higher brain activation, the antisocial traits are less severe, but are still more pronounced than in the nonviolent groups.

Thus, these 2 sets of psychopathic traits have different antecedents and are dissociable at the neural level. The affective-interpersonal symptoms represent core psychopathic traits caused by neural dysfunctions, whereas the antisocial/impulsive traits have a more heterogenous etiology; neural impairment acts against a background of other etiological factors to influence these traits.

These findings are consistent with reports in the literature on psychopathy that neurophysiological factors are more strongly associated with the first than second PCL factor. One study[64] found that the first factor, but not the second, was related to brain dysfunction in multiple brain areas. In other studies, higher scores on PCL Factor 1 but not Factor 2 were associated with reduced gray matter volume.[65,66] These differences between the 2 factors have been reported in nonpsychotic populations, but not in patients with schizophrenia.

Relationship Between the Antisocial Traits and Developmental/Educational Factors

Developmental and educational factors are associated with antisocial/impulsive traits. In our data, we found an inverse relationship between reading ability, which is a good measure of educational achievement, and these traits; this is consistent with the literature mentioned above.[10] There was no relationship between reading ability and the first factor.

Thus, in subjects with schizophrenia, even when there is better brain function, and less interpersonal-affective dysfunction, antisocial traits and behaviors may still be present and lead to violence.

Strengths and Limitations of the Study

A limitation of this study is its potential lack of generalizability to some patient populations. Subjects had to sign consent which included permission to access criminal records; it is therefore possible that more suspicious, hostile, or psychopathic subjects were not willing to participate. Some of the participants had difficulty with the task and were excluded. While they did not differ from the retained subjects in basic demographic and clinical data, this fact may still limit the generalizability of our findings.

Finally, the IAPS includes valenced and neutral pictures but we focused the analyses for this investigation on neutral ones to reduce heterogeneity. This may not be equivalent to presenting only neutral pictures for the purpose of investigating basic inhibition processes.

The strengths of the study include the inclusion of violent subjects without any psychosis, the selection of well-defined violent and nonviolent groups, as the inclusion criteria were not based on self-report alone. Furthermore, these criteria allowed us to identify a persistently violent group of subjects. The findings of this study on the violent patients with schizophrenia are new and have not been reported before.

Conclusions

Our study provides important information about the role of neural dysfunction for psychopathic traits

in schizophrenia. These findings have important implications for the conceptualization of violence in schizophrenia and for its treatment. These traits must be assessed as part of the evaluation of violence in patients with schizophrenia. As they are distinct from the psychotic symptoms, aggression in patients with psychopathic traits may not respond adequately to pharmacotherapy alone and may require adjunctive psychosocial treatments.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin Open* online.

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The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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