HHS Public Access

Author manuscript

Curr Opin Psychiatry. Author manuscript; available in PMC 2015 April 30.

Published in final edited form as:

Curr Opin Psychiatry. 2011 March ; 24(2): 100–106. doi:10.1097/YCO.0b013e328342c8e0.

Neuroimaging correlates of aggression in schizophrenia: an update

Matthew J. Hoptman[a,b] and **Daniel Antonius**[c]

[a]Schizophrenia Research Division, Nathan S. Kline, Institute for Psychiatric Research, Orangeburg, New York, New York, USA

[b]Department of Psychiatry, NYU School of Medicine, New York, New York, USA

[c]Department of Psychiatry, Institute for Social and Psychiatric Initiatives (InSPIRES), NYU School of Medicine, New York, New York, USA

Abstract

Purpose of review—Aggression in schizophrenia is associated with poor treatment outcomes, hospital admissions, and stigmatization of patients. As such it represents an important public health issue. This article reviews recent neuroimaging studies of aggression in schizophrenia, focusing on PET/single photon emission computed tomography and MRI methods.

Recent findings—The neuroimaging literature on aggression in schizophrenia is in a period of development. This is attributable in part to the heterogeneous nature and basis of that aggression. Radiological methods have consistently shown reduced activity in frontal and temporal regions. MRI brain volumetric studies have been less consistent, with some studies finding increased volumes of inferior frontal structures, and others finding reduced volumes in aggressive individuals with schizophrenia. Functional MRI studies have also had inconsistent results, with most finding reduced activity in inferior frontal and temporal regions, but some also finding increased activity in other regions. Some studies have made a distinction between types of aggression in schizophrenia in the context of antisocial traits, and this appears to be useful in understanding the neuroimaging literature.

Summary—Frontal and temporal abnormalities appear to be a consistent feature of aggression in schizophrenia, but their precise nature likely differs because of the heterogeneous nature of that behavior.

Keywords

aggression; MRI; schizophrenia; violence

Correspondence to Matthew J. Hoptman, PhD, Nathan Kline Institute for Psychiatric Research, 140 Old Orangeburg Road, Building 35, Orangeburg, New York, USA, Tel: +1 845 398 6569; fax: +1 845 398 6566; hoptman@nki.rfmh.org.

There are no conflicts of interest.

Introduction

Violence and aggression are serious public health concerns [1], and are linked with severe mental illness [1–3], particularly schizophrenia [4–6]. Patients with schizophrenia show modestly increased levels of aggression relative to the general population [2,4], which is increased with comorbid substance use [7,8]. This violence may cause physical and psychological damage to patients and victims, and precipitate admissions to hospitals and forensic institutions, or prevent discharge from such institutions [9]. This adds to the enormous economic cost of schizophrenia [10]. Moreover, the media tends to sensationalize violence in the mentally ill [11], leading to the public conception that schizophrenia is a 'violent disorder', thereby increasing stigma [12,13].

It is therefore important to move toward a better understanding of the salient neurobiology underlying violence and aggression in schizophrenia. Such research can inform novel treatments and may begin to address several of the public health problems associated with aggression in schizophrenia.

In the current article, we will review the recent literature on the neuroimaging correlates of aggression in schizophrenia. It should be noted, however, that other domains have been quite informative, including neuropsychological [14] and psychopharmacological [15,16] studies. Before we review the neuroimaging literature, we will first address some conceptual issues that are crucial to progress in the field.

Measures of aggression

Much of the violence data in schizophrenia come from self-report, which poses significant problems because of the unreliability of such report, particularly in clinical populations. Behavioral measures of aggression, such as the Point Subtraction Aggression Paradigm [17] or the Taylor Aggression Paradigm [18], which might provide more fine-grained information than self-report measures, have not been widely employed in patients with schizophrenia, and certainly not in the context of neuroimaging.

Heterogeneity of aggression

Another key issue is that violence in schizophrenia is heterogeneous: some violence is psychosis-related and can be reduced with antipsychotic medication [19,20]; other aggression is driven by personality traits, is independent of psychosis, and does not wane with standard treatments [21,22]. Some studies have focused on habitually violent patients, who represent only a fraction of aggressive patients. Moreover, habitually violent patients appear to differ neurobiologically from those who are only transiently violent [23].

Researchers postulate several different developmental pathways to aggressive behavior in schizophrenia. Swanson *et al.* [21] suggested two pathways: one related to psychotic symptoms exhibited in adulthood, and another related to antisocial problems in childhood. Hodgins [24] postulated three pathways: lifetime antisocial behavior; aggression that commences at psychosis/illness onset; and aggression that begins years after onset. The antisocial subgroup, which includes the habitually more violent patients, is more likely to

engage in violence [21,25], has an earlier first hospitalization, and longer stays in hospitals [25]. In another triarchic model, Krakowski [26] distinguishes among patients who are transiently violent and show symptoms of excitation and hyperarousal, persistently violent patients with minimal neurological impairment, and persistently violent patients with prominent neurological deficits and negative symptoms.

Psychosis alone is not sufficient to explain differences in violence rates between people with schizophrenia and the general population. Rather, psychosis is one of several risk factors for violence in schizophrenia [27]. The literature further suggests that violence and psychosis may be orthogonal. Preliminary cognitive [14,22] and neuroimaging [28•] reports suggest that there are neurobiological differences between people from the different violence pathways.

A relatively new avenue of neurobiological research focuses on the subfeatures of callousness and unemotionality (callous-unemotional traits). Those with callous-unemotional traits represent a subgroup that is at particularly high risk for pervasive violent and criminal behavior [29]. Studies of children and adolescents suggest the involvement of specific neural circuitry deficits in the amygdala and ventromedial prefrontal cortex. Recently, callous-unemotional traits were proposed as a key characteristic of the forthcoming Diagnostic and Statistical Manual of Mental Disorders - V (DSM-V) antisocial personality type [30]. Despite this knowledge, and reports of a core subgroup of violent schizophrenia patients with these features [31,32], no research has examined the neurobiology of callous-unemotional traits in schizophrenia.

Having covered two of the main conceptual hurdles to understanding the neural basis of aggression in schizophrenia, we turn to a review of recent neuroimaging results. These results are summarized in Table 1.

PET/single photon emission computed tomography studies

Some of the earliest studies of aggression in schizophrenia come from radiological methods such as positron emission tomography (PET). Raine *et al.* [33•,34] studied accused murderers pleading not guilty by reason of insanity and age and sex-matched controls using performance on a continuous performance task (CPT). Accused murderers had reduced glucose metabolism in the prefrontal region, superior parietal region, angular gyrus, and corpus callosum, along with abnormal metabolic asymmetries (right > left) in numerous regions during the CPT. In a subsequent analysis of these data, Raine *et al.* [35••] found a greater reduction in frontal activation in those with affective rather than predatory basis crimes.

In a single photon emission computed tomography (SPECT) comparing three aggressive with 12 nonaggressive schizophrenia patients during a cognitive set-shifting task (the Wisconsin Card Sorting Task), Spaletta *et al*. [36] found reduced prefrontal regional cerebral blood flow in the aggressive patients only. No difference was found between groups when not presented with a task (at rest).

In an early study on male patients with schizophrenia, Wong *et al.* [37] found reduced fluoro-deoxyglucose (FDG) uptake in the left and right anterior inferior temporal region in patients with nonrepetitive violent offending, but only in the left anterior inferior temporal region in patients with repetitive violent offending. However, this study has not been replicated. Thus, although findings with PET and SPECT are fairly consistent with respect to brain regions implicated in aggression, the findings specific to schizophrenia are limited.

MRI studies

MRI studies of aggression in schizophrenia have fallen into two main categories. Structural MRI studies have focused on brain volumetric measures and white matter integrity, whereas functional MRI studies have focused on patterns of brain activation either during a task or at rest.

Structural MRI

In a meta-analysis, Yang and Raine [46] found that cortical volumes were reduced in antisocial, psychopathic, and violent populations. Among these are studies showing reduced frontal gray matter but not white matter in violent patients with antisocial personality disorder [47•]. However, Hoptman *et al.* found that aggression in patients with treatment-resistant schizophrenia or schizoaffective disorder was associated with larger caudate [38] and orbitofrontal (OFC) [39] volumes. They attributed these findings to long-term ineffective treatment with typical antipsychotic medication, based on findings that these agents increase basal ganglia (and possibly other) volumes both in patients [48,49] and in the rat [50]. Similarly, Rüsch *et al.* [40] found that larger OFC volumes were associated with a history of suicide attempts in patients with schizophrenia. It is possible that this finding was due to the effect of antipsychotics, but medication histories were not reported in this article.

Larger regional brain volumes in populations noted for aggression are not limited to schizophrenia, as Glenn *et al.* [51] reported larger striatal volumes in psychopaths than in healthy controls. Moreover, in a whole-brain voxel-based morphometry (VBM) study, De Brito *et al.* [52] found larger gray matter volumes in boys with callous-unemotional conduct problems in medial orbitofrontal, anterior cingulate regions and higher gray matter concentrations in the temporal lobes bilaterally compared with healthy controls. They attributed these findings to delayed cortical maturation of these areas, which are critical to the pathology seen in this group.

Tiihonen *et al.* [53], in a study of persistent violent offenders with antisocial personality disorder and substance dependence, but without schizophrenia, found larger white matter volumes in occipital and parietal lobe and right cerebellum, and greater gray matter volumes in left cerebellum. However, using VBM, they found reduced gray matter volumes in postcentral gyrus, frontopolar cortex and orbitofrontal cortex. It is unclear why the authors chose to focus on white matter volumes when they also found changes in the opposite direction for gray matter (albeit using different methods). It is worth considering that image tissue contrast differences could account for relative shifts in the classification of tissue as gray matter vs. white matter, which would lead to opposite effects for the two tissue types.

Cortical thickness also appears to be reduced in aggressive patients with schizophrenia. In a study of aggressive and nonaggressive patients with either antisocial personality disorder or schizophrenia, Narayan *et al.* [41•] found reduced cortical thickness in ventromedial prefrontal and lateral sensorimotor cortex in the aggressive compared with nonaggressive patients, especially in the right hemisphere. Within aggressive patients, however, only those with antisocial personality disorder (as opposed to schizophrenia) showed reduced thickness in the medial frontal cortex.

Finally, there is some evidence of white matter abnormalities associated with aggression in schizophrenia. In a diffusion tensor imaging (DTI) study, Hoptman *et al.* [42] found that levels of aggression, as measured by the Life History of Aggression [54] and Buss Durkee Hostility Inventory [55], were associated with increased diffusivity in inferior frontal white matter. Increased diffusivity has been associated with atrophy in schizophrenia [56], and specifically with increased cerbrospinal fluid (CSF) volumes [57].

The structural MRI literature thus far suggests that brain volumetric measures can be either larger or smaller in aggressive patients with schizophrenia. We are aware of only one published cortical thickness paper, which was inconclusive regarding aggression in schizophrenia. The only DTI study on aggression in schizophrenia supports the idea that white matter disruptions in ventral prefrontal white matter are associated with aggressive attitudes and history.

Functional MRI

Few functional MRI (fMRI) studies have examined aggressive patients with schizophrenia. For this reason, we will also discuss studies in nonschizophrenia populations. In the first study of its kind, Kiehl *et al.* [58] found reduced activation in limbic regions (amygdala, hippocampus, parahippocampus, striatum, and cingulate) in the memory of affective words in eight criminal psychopaths compared with eight noncriminal psychopaths and eight healthy controls. The criminal psychopaths showed increased activation in frontotemporal cortex. Raine *et al.* [59] found that severely abused violent offenders had lower activation in the right hemisphere, particularly right temporal regions, during a visual verbal working memory test compared with severely abused nonviolent ones. In a study of aversive delay conditioning, Veit *et al.* [60] found reduced activation in the bilateral orbitofrontal cortex, insula, and anterior cingulate, as well as right amygdala and left dorsolateral prefrontal cortex, in psychopaths compared with healthy controls. A group of people with social phobia showed increased activity in these same regions compared with controls.

More recently, fMRI studies have examined the neural correlates of callous-unemotional traits in violent populations. These studies, in which imaging is conducted while individuals are performing emotional processing tasks, implicate amygdala hypoactivation and compromised amygdala-ventromedial prefrontal cortex regions in those with higher levels of callous-unemotional traits [61,62••].

In a study of violent patients with schizophrenia and comorbid antisocial personality disorder and substance use disorders, Joyal *et al.* [43•] examined blood oxygen level dependent (BOLD) response during a go/no-go task that examines response inhibition. They

found that patients with comorbid antisocial personality disorder and substance use disorders showed decreased frontal basal activation compared with aggressive patients with schizophrenia only and with nonviolent healthy controls. The comorbid group also showed increased activity in motor, premotor, and anterior cingulate regions. They suggested that antisocial patients have abnormalities in ventral frontal regions, whereas those without such comorbidity might be more characterized by executive dysfunctions in more dorsal frontal regions.

Kumari *et al.* [44••] demonstrated abnormalities in activity modulation in occipital-temporal regions during an anticipatory fear task in violent individuals with schizophrenia and people with antisocial personality disorder, compared with nonviolent control groups. Within the violent groups, however, the violent schizophrenia patients demonstrated hyperactivity in the thalamic–striatal area, whereas the antisocial patients showed hypoactivity in the same area. The authors speculate that these opposite neural findings may reflect distinct threat–response behavioral mechanisms.

In the only fMRI study on distinct violence-prone schizophrenia subgroups, Dolan and Fullam [28•] examined neural responses to emotional faces in schizophrenia individuals high and low on psychopathic traits. The findings suggest that individuals with higher psychopathy scores exhibit compromised amygdala–prefrontal cortex functioning, and attenuated amygdala activation when presented with fearful faces. Moreover, these results support the notion that a subgroup of violent schizophrenia individuals with persistent, life-long antisocial/psychopathic traits is characterized by distinct neural circuit abnormalities. These results should be interpreted with caution, however. Dolan and Fullam [28•] used a relatively small sample of only male patients, and had no nonschizophrenia control population.

Functional connectivity is defined as the temporal correlation of activity in disparate regions [63]. Biswal *et al.* [64] were the first to show that such activity exists even in the absence of an overt task. This observation is valuable because it gets around the influence of task performance on brain activation or functional connectivity. Thus far, only one study has been published on resting state functional connectivity (RSFC) and aggression in patients with schizophrenia. In that study, Hoptman *et al.* [45•] examined functional connectivity with the amygdala on a voxelwise basis in 25 patients with schizophrenia and 21 healthy controls. The seeds used to examine this functional connectivity were derived from an anatomically validated study of effective connectivity of the amygdala [65]. Compared with controls, patients showed significant reductions in functional connectivity between the amygdala and ventral prefrontal cortex. More importantly for the current discussion, this reduction, which trended toward negative functional connectivity, predicted higher levels of aggression on two different measures. The effect was not related to neuroleptic medication dosage or to age, and was specific to the amygdala, as it was not observed in networks associated with the dorsolateral prefrontal cortex, OFC, or supragenual or subgenual cingulate.

It will be interesting to see whether these findings are related to direct structural connectivity impairment or if they are driven by some other set of regions. However, the findings of this

study are consistent with DTI findings, reported above, which suggest reduced white matter integrity in the inferior frontal regions in schizophrenia is associated with aggression. It is of particular note that the white matter regions interrogated in the DTI study contain fibers of the uncinate fasciculus, which connects the amygdala with the ventral prefrontal cortex regions [66], areas implicated in the resting state study.

Conclusion

Research on the neural basis of aggression in schizophrenia suggests the involvement of abnormal frontotemporal circuitry. The few PET/SPECT studies focusing on schizophrenia have shown reduced activity in those regions. Brain volumetric measures have been less consistent, with some studies showing increased volumes in more aggressive schizophrenia patients. Functional imaging studies have been consistent in showing abnormalities in the ventral prefrontal regions, with less consistent patterns in other regions.

Progress has been hampered by the dearth of critical studies in the area. The specificity with respect to the heterogeneity of schizophrenia is limited because numerous studies employ patients from multiple diagnostic categories. Another area that is poorly understood is the cause of aggression in schizophrenia. Aggressive acts can have numerous bases, including impulsivity, psychotic misinterpretation, and purely instrumental bases. Often, these different causes occur within the same aggressive act [32].

It will be important to develop strategies to better understand how these different causes interact and whether they are separable. In addition, imaging studies are still fairly limited. Multimodal imaging studies that combine structural and functional components in the same individuals are likely to be most fruitful, but are lacking. Studies combining better characterization of clinical populations, better understanding of the cause of aggressive acts, and more coherent imaging strategies will likely be conducted in the next several years.

Acknowledgements

The work was supported by R01 MH064783 and R21 MH084031 to M.J.H.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 173).

1. Hodgins S, Alderton J, Cree A, et al. Aggressive behaviour, victimization and crime among severely mentally ill patients requiring hospitalisation. Br J Psychiatry. 2007; 191:343–350. [PubMed: 17906245]
2. Teplin LA, McClelland GM, Abram KM, Weiner DA. Crime victimization in adults with severe mental illness: comparison with the National Crime Victimization Survey. Arch Gen Psychiatry. 2005; 62:911–921. [PubMed: 16061769]

3. Swanson J, Holzer C III, Ganju V, Tsutumo Jono R. Violence and psychiatric disorder in the community: evidence from the epidemiologic catchment area survey. Hosp Commun Psychiatry. 1990; 41:761–770.
4. Walsh E, Buchanan A, Fahy T. Violence and schizophrenia: examining the evidence. Br J Psychiatry. 2002; 180:490–495. [PubMed: 12042226]
5. Swanson JW, Swartz MS, Van Dorn RA, et al. A national study of violent behavior in persons with schizophrenia. Arch Gen Psychiatry. 2006; 63:490–499. [PubMed: 16651506]
6. Fazel S, Langstrom N, Hjern A, et al. Schizophrenia, substance abuse, and violent crime. JAMA. 2009; 301:2016–2023. [PubMed: 19454640]
7. Swanson, JW. Mental disorder, substance abuse, and community violence: an epidemiological approach. In: Monahan, J.; Steadman, HJ., editors. Violence and mental disorder: developments in risk assessment. Chicago, IL: University of Chicago Press; 1994. p. 101-136.
8. Steadman HJ, Mulvey EP, Monahan J, et al. Violence by people discharged from acute psychiatric inpatient facilities and by others in the same neighborhoods. Arch Gen Psychiatry. 1998; 55:393–401. [PubMed: 9596041]
9. Volavka, J. Neurobiology of violence. 2nd ed.. Washington, DC: APA Publishing; 2002.
10. McEvoy JP. The costs of schizophrenia. J Clin Psychiatry. 2007; 68(Suppl 14):4–7. [PubMed: 18284271]
11. Ferriman A. The stigma of schizophrenia. BMJ. 2000; 320:522. [PubMed: 10678889]
12. Link BG, Phelan JC, Bresnahan M, et al. Public conceptions of mental illness: labels, causes, dangerousness, and social distance. Am J Public Health. 1999; 89:1328–1333. [PubMed: 10474548]
13. Van Dorn RA, Swanson JW, Elbogen EB, Swartz MS. A comparison of stigmatizing attitudes toward persons with schizophrenia in four stakeholder groups: perceived likelihood of violence and desire for social distance. Psychiatry. 2005; 68:152–163. [PubMed: 16247858]
14. Schug RA, Raine A. Comparative meta-analyses of neuropsychological functioning in antisocial schizophrenic persons. Clin Psychol Rev. 2009; 29:230–242. [PubMed: 19278761]
15. Swanson JW, Swartz MS, Van Dorn RA, et al. Comparison of antipsychotic medication effects on reducing violence in people with schizophrenia. Br J Psychiatry. 2008; 193:37–43. [PubMed: 18700216]
16. Volavka J, Czobor P, Nolan K, et al. Overt aggression and psychotic symptoms in patients with schizophrenia treated with clozapine, olanzapine, risperidone, or haloperidol. J Clin Psychopharmacol. 2004; 24:225–228. [PubMed: 15206671]
17. Cherek, DR. A manual for the Point Subtraction Aggression Paradigm. Houston, TX: University of Texas, Houston; 1992.
18. Taylor S. Aggressive behavior and physiological arousal as a function of provocation and the tendency to inhibit aggression. J Personality. 1967; 35:297–310. [PubMed: 6059850]
19. Buckley PF, Wirshing DA, Bhushan P, et al. Lack of insight in schizophrenia: impact on treatment adherence. CNS Drugs. 2007; 21:129–141. [PubMed: 17284095]
20. Swanson JW, Swartz MS, Elbogen EB. Effectiveness of atypical antipsychotic medications in reducing violent behavior among persons with schizophrenia in community-based treatment. Schizophr Bull. 2004; 30:3–20. [PubMed: 15176758]
21. Swanson JW, Van Dorn RA, Swartz MS, et al. Alternative pathways to violence in persons with schizophrenia: the role of childhood antisocial behavior problems. Law Hum Behav. 2008; 32:228–240. [PubMed: 17602288]
22. Naudts K, Hodgins S. Neurobiological correlates of violent behavior among persons with schizophrenia. Schizophr Bull. 2006; 32:562–572. [PubMed: 16384876]
23. Krakowski M, Czobor P, Chou JC. Course of violence in patients with schizophrenia: relationship to clinical symptoms. Schizophr Bull. 1999; 25:505–517. [PubMed: 10478785]
24. Hodgins S. Violent behaviour among people with schizophrenia: a framework for investigations of causes, and effective treatment, and prevention. Philos Trans R Soc Lond B Biol Sci. 2008; 363:2505–2518. [PubMed: 18434282]

25. Hodgins S, Tiihonen J, Ross D. The consequences of conduct disorder for males who develop schizophrenia: associations with criminality, aggressive behavior, substance use, and psychiatric services. Schizophr Res. 2005; 78:323–335. [PubMed: 15996855]
26. Krakowski M. Schizophrenia with aggressive and violent behaviors. Psychiatric Annals. 2005; 35:45–49.
27. Siever LJ. Neurobiology of aggression and violence. Am J Psychiatry. 2008; 165:429–442. [PubMed: 18346997]
28. Dolan MC, Fullam RS. Psychopathy and functional magnetic resonance imaging blood oxygenation level-dependent responses to emotional faces in violent patients with schizophrenia. Biol Psychiatry. 2009; 66:570–577. [PubMed: 19446795] This study examines the role of psychopathy in an fMRI study of violent patients with schizophrenia. It highlights the heterogeneity of aggression in considering the role of comorbid psychopathy.
29. Frick PJ, White SF. Research review: the importance of callous-unemotional traits for developmental models of aggressive and antisocial behavior. J Child Psychol Psychiatry. 2008; 49:359–375. [PubMed: 18221345]
30. American Psychiatric Association. Antisocial personality disorder. Washington, DC: American Psychiatric Association; 2010.
31. Sunak, S. Deficient affective experience and violence in schizophrenia. London: King's College; 2006.
32. Nolan KA, Czobor P, Roy BB, et al. Characteristics of assaultive behavior in psychiatric inpatients. Psychiatric Serv. 2003; 54:1012–1016.
33. Raine A, Buchsbaum MS, Stanley J, et al. Selective reductions in prefrontal glucose metabolism in murderers. Biol Psychiatry. 1994; 36:365–373. [PubMed: 7803597] This is an important early study on glucose metabolism in murderers. It has stimulated much of the subsequent research.
34. Raine A, Buchsbaum M, LaCasse L. Brain abnormalities in murderers indicated by positron emission tomography. Biol Psychiatry. 1997; 42:495–508. [PubMed: 9285085]
35. Raine A, Meloy JR, Bihrle S, et al. Reduced prefrontal and increased subcortical brain functioning assessed using positron emission tomography in predatory and affective murderers. Behav Sci Law. 1998; 16:319–332. [PubMed: 9768464] This study is the first neuroimaging study to dissociate between predatory and affective bases of aggressive behavior, and thus gets at important issues in heterogeneity of aggression.
36. Spalletta G, Troisi A, Alimenti S, et al. Reduced prefrontal cognitive activation associated with aggression in schizophrenia. Schizophr Res. 2001; 60:134–135. [PubMed: 11426431]
37. Wong MTH, Fenwick PBC, Lumsden J, et al. Positron emission tomography in male violent offenders with schizophrenia. Psychiatry Res Neuroimag. 1997; 68:111–123.
38. Hoptman MJ, Volavka J, Czobor P, et al. Aggression and quantitative MRI measures of caudate in chronic schizophrenia and schizoaffective disorder. J Neuropsychiatry Clin Neurosci. 2006; 18:509–515. [PubMed: 17135376]
39. Hoptman MJ, Volavka J, Weiss EM, et al. Quantitative MRI measures of orbitofrontal cortex in patients with chronic schizophrenia or schizoaffective disorder. Psychiatry Res Neuroimag. 2005; 140:133–145.
40. Rüsch N, Spoletini I, Wilke M, et al. Inferior frontal white matter volume and suicidality in schizophrenia. Psychiatry Res. 2008; 164:206–214. [PubMed: 19008082]
41. Narayan VM, Narr KL, Kumari V, et al. Regional cortical thinning in subjects with violent antisocial personality disorder or schizophrenia. Am J Psychiatry. 2007; 164:1418–1427. [PubMed: 17728428] This study is, to date, the only one to examine cortical thickness in violent patients with antisocial personality disorder and/or schizophrenia.
42. Hoptman MJ, Volavka J, Johnson G, et al. Frontal white matter, aggression and impulsivity in men with schizophrenia. Biol Psychiatry. 2002; 52:9–14. [PubMed: 12079725]
43. Joyal CC, Putkonen A, Mancini-Marie A, et al. Violent persons with schizophrenia and comorbid disorders: a functional magnetic resonance imaging study. Schizophr Res. 2007; 91:97–102. [PubMed: 17291724] This study examines the important role of comorbidity in aggression in schizophrenia.

44. Kumari V, Das M, Taylor PJ, et al. Neural and behavioural responses to threat in men with a history of serious violence and schizophrenia or antisocial personality disorder. Schizophr Res. 2009; 110:47–58. [PubMed: 19230621] This is an important study because it divides patients into antisocial personality disorder with and without schizophrenia, thereby explicitly considering heterogeneity of aggression.
45. Hoptman MJ, D'Angelo D, Catalano D, et al. Amygdalofrontal functional connectivity and aggression in schizophrenia. Schizophrenia Bull. 2010; 36:1020–1028. This study is the only functional connectivity study of aggression in schizophrenia and suggests a role for abnormalities in frontotemporal connectivity in this behavior.
46. Yang Y, Raine A. Prefrontal structural and functional brain imaging findings in antisocial, violent, and psychopathic individuals: a meta-analysis. Psychiatry Res. 2009; 174:81–88. [PubMed: 19833485]
47. Raine A, Lencz T, Bihrle S, et al. Reduced prefrontal gray matter volume and reduced autonomic activity in antisocial personality disorder. Arch Gen Psychiatry. 2000; 57:119–127. [PubMed: 10665614] This is the first study to show abnormal prefrontal brain volumes in patients with antisocial personality disorder. It provides an anatomical context for the groups' earlier findings of reduced glucose metabolism in prefrontal regions.
48. Keshavan MS, Bagwell WW, Haas GL, et al. Changes in caudate volume with neuroleptic treatment. Lancet. 1994; 344:1434. [PubMed: 7968091]
49. Chakos MH, Lieberman JA, Bilder RM, et al. Increase in caudate nuclei volumes of first-episode schizophrenic patients taking antipsychotic drugs. Am J Psychiatry. 1994; 151:1430–1436. [PubMed: 7916539]
50. Lee H, Tarazi FI, Chakos M, et al. Effects of chronic treatment with typical and atypical antipsychotic drugs on the rat striatum. Life Sci. 1999; 64:1595–1602. [PubMed: 10328519]
51. Glenn AL, Raine A, Yaralian PS, Yang Y. Increased volume of the striatum in psychopathic individuals. Biol Psychiatry. 2010; 67:52–58. [PubMed: 19683706]
52. De Brito SA, Mechelli A, Wilke M, et al. Size matters: increased grey matter in boys with conduct problems and callous-unemotional traits. Brain. 2009; 132:843–852. [PubMed: 19293245]
53. Tiihonen J, Rossi R, Laakso MP, et al. Brain anatomy of persistent violent offenders: more rather than less. Psychiatry Res. 2008; 163:201–212. [PubMed: 18662866]
54. Coccaro EF, Berman ME, Kavoussi RJ. Assessment of life history of aggression: development and psychometric characteristics. Psychiatry Res. 1997; 73:147–157. [PubMed: 9481806]
55. Buss A, Durkee A. An inventory for assessing different kinds of hostility. J Consulting Psychol. 1957; 21:343–349.
56. Ardekani BA, Bappal A, D'Angelo D, et al. Brain morphometry using diffusion-weighted magnetic resonance imaging: application to schizophrenia. NeuroReport. 2005; 16:1455–1459. [PubMed: 16110271]
57. Narr KL, Hageman N, Woods RP, et al. Mean diffusivity: a biomarker for CSF-related disease and genetic liability effects in schizophrenia. Psychiatry Res. 2009; 171:20–32. [PubMed: 19081707]
58. Kiehl KA, Smith AM, Hare RD, et al. Limbic abnormalities in affective processing by criminal psychopaths as revealed by functional magnetic resonance imaging. Biol Psychiatry. 2001; 50:677–684. [PubMed: 11704074]
59. Raine A, Park S, Lencz T, et al. Reduced right hemisphere activation in severely abused violent offenders during a working memory task: an fMRI study. Aggressive Behav. 2001; 27:111–129.
60. Veit R, Flor H, Erb M, et al. Brain circuits involved in emotional learning in antisocial behavior and social phobia in humans. Neurosci Lett. 2002; 328:233–236. [PubMed: 12147314]
61. Jones AP, Laurens KR, Herba CM, et al. Amygdala hypoactivity to fearful faces in boys with conduct problems and callous-unemotional traits. Am J Psychiatry. 2009; 166:95–102. [PubMed: 18923070]
62. Marsh AA, Finger EC, Mitchell DG, et al. Reduced amygdala response to fearful expressions in children and adolescents with callous-unemotional traits and disruptive behavior disorders. Am J Psychiatry. 2008; 165:712–720. [PubMed: 18281412] This is the first neuroimaging article to examine the nature of callous-unemotional behavior.

63. Friston KJ. Functional and effective connectivity in neuroimaging: a synthesis. Human Brain Mapping. 1994; 2:56–78.

64. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med. 1995; 34:537–541. [PubMed: 8524021]

65. Stein JL, Wiedholz LM, Bassett DS, et al. A validated network of effective amygdala connectivity. Neuroimage. 2007; 36:736–745. [PubMed: 17475514]

66. Schmamann, JD.; Pandya, DN. Fiber pathways of the brain. New York: Oxford University Press; 2006.

Table 1

Summary of studies on PET and MRI and aggression in schizophrenia

Study	*N*[a]	Age (years)[b]	Sex (M/F)	Psychiatric status[c]	Results[d]
PET					
Spalletta *et al.* Spaletta *et al*. [36]	15	Range 18–65	Not reported	SZ	Aggressive patients (*N* = 3) showed reduced prefrontal (right middle and right inferior prefrontal gyri) rCBF during the Wisconsin Card Sorting Task.
Wong *et al.* [37]	37	Mean ages range from 35.2 to 40.4 years	Not reported	17 SZ/SZA + VO; 14 SZ/SZA − VO; six controls	Reduced FDG uptake in the left and right anterior inferior temporal regions in nonrepetitive violent patients, but only in the left anterior inferior temporal region in repetitive violent patients.
MRI					
Structural					
Hoptman *et al*. [38]	49	41.5 ± 8.2	43/6	SZ/SZA	Larger left and right caudate volumes associated with higher levels of aggression during a 14-week study period.
Hoptman *et al*. [39]	49	41.5 ±8.2	43/6	SZ/SZA	Larger left OFC volumes and larger right OFC WM volumes correlated with higher levels of aggression during a 14-week study period.
Rusch *et al.* [40]	105	WS: 30.3 ± 6.5; W/O: 37.3 ± 11.6	WS: 7/3; W/O: 27/18	10 SZ + suicide attempts; 45 SZ − suicide attempts	Patients with suicide attempts had larger OFC volumes.
Narayan *et al.* [41•]	56	Means range from 32.1 to 34.5 years	All males	12 SZ + V; 15 SZ − V; 14 ASPD + V; 15 controls	Reduced whole-brain gray matter in schizophrenia and violence compared with controls. Reduced cortical thickness in vmPFC and lateral sensorimotor areas in aggressive vs. nonaggressive patients, particularly in right hemisphere. Within aggressive patients, only ASPD showed reduced thickness in medial PFC.
Hoptman *et al*. [42]	14	40.5 ± 7.8	All males	SZ/SZA	Mean diffusivity in inferior frontal regions was associated with higher levels of self-reported aggression.
Functional					
Joyal *et al*. [43•]	36	28–54 years	All males	12 SZ + V; 12 SZ + ASPD + SUD; 12 controls	During a go/no-go task, patients with comorbid ASPD and SUD showed decreased frontal basal activation compared with aggressive patients. Comorbid group also had higher activity in motor, prefrontal and anterior cingulate regions.
Kumari *et al.* [44••]	53	Means range from 32.85 to 34.46 years	All males	13 SZ +V; 13 SZ −V; 13 ASPD +V; 14 controls	During an anticipatory fear paradigm, SZ +V and ASPD groups showed abnormal activity modulation in occipital–temporal regions. Within violent groups, SZ + V showed hypereactivity, and ASPD + V showed hypoactivity, in thalamic–striatal regions.
Dolan and Fullam [28•]	24	Means range from 35.92 to 40.67 years	All males	SZ + high psychopathy; SZ + low psychopathy	During exposure to emotional faces, patients high on psychopathy had decreased activation in right amygdala during exposure to fearful faces and increased activation in the right amygdala during exposure to disgust faces.
Hoptman *et al*. [45•]	46	P: 40.4 ± 10.8; C: 36.7 ± 10.5	SZ: 22/3; C: 16/5	SZ/SZA	Reduced functional connectivity between amygdala and ventral prefrontal regions in patients. Reduction was associated with higher levels of aggression in patients.

[a] Number of participants.

[b] P, patients; C, controls; WS, with suicide attempts; W/O, without suicide attempts.

[c] SZ, schizophrenia; SZA, schizoaffective disorder; ASPD, antisocial personality disorder; V, violence; VO, violent offenders.

[d] rCBF, regional cerebral blood flow; FDG, fluorodeoxyglucose; OFC, orbitofrontal cortex; SUD, substance use disorder; vmPFC, ventromedial prefrontal cortex.