Neuroimaging violence in the mentally ill: what can it tell us?

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Incidents of aggression and violence in severe mental disorders like psychosis, personality disorders and substance misuse disorders are higher than in the general population. Recent advances in neuroimaging techniques may help to predict violent behaviour in mentally ill individuals and to identify anomalies in brain functioning that may be amenable to treatment.

There is evidence to suggest that there is an over-representation of antisocial behaviour such as violent crime and homicide among the mentally ill, in those suffering such mental illness such as schizophrenia, substance misuse and personality disorders. A review carried out by Angermeyer (2001) cites several sources which showed that having a mental illness elevated the relative risk of violence. However, the violence is not usually directed at strangers but more towards people who are in close contact with the patient and, thus, has implications for the clinical care and management of people with mental illnesses. There is a pressing need to pursue research into the aetiology and effects of violence in the mentally ill. The ramifications for such research are likely to extend from clinical management, prevention and risk assessment, up to stigma reduction and resource allocation.

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VIOLENCE IN MENTAL ILLNESS

Statistics and figures

Between 8 and 10% of people with schizophrenia have had violent episodes (not necessarily serious ones) in a 12-month period compared to 2% in the general population (Swanson et al, 1990). Between March 2000 and March 2001 the Home Office reported that nearly 700 000 offences had occurred in England and Wales that were of a 'violent nature' (violence against the person, sexual offences and robbery) (Povey, 2001). In the year 2000, 319 restricted patients (mentally ill) were admitted to hospitals for violence towards persons (including homicide or murder) (Johnson and Taylor, 2000). As a basic comparison, only 13% of offences in the general population are of a violent nature, whereas nearly half (47%) of those admitted under hospital orders were convicted or charged of violence.

In the national confidential inquiry into suicide and homicide by people with mental illness (Shaw et al, 1999), of the 718 homicides reported to the inquiry between April 1996 and November 1997 in England and Wales, 14% had symptoms of mental illness at the time of the homicide. In a study from the United States (Steadman et al, 1998) examining prevalence of community violence in people in the year after discharge from acute psychiatric facilities, the 1-year prevalence of violence was 17.9% for patients with a major mental disorder and without a substance abuse diagnosis and 31.1% for patients with major mental disorder and a substance abuse diagnosis. There was no significant difference between the prevalence of violence by patients without symptoms of substance abuse and the prevalence of violence by others living in the same neighbourhood who were also without symptoms of substance misuse.

The relative number of violent crimes carried out by those considered mentally ill is small in comparison to the general population. However, research into this issue is still imperative as violence in the mentally ill has a range of implications.

Specific disorders implicated in violence

Among the severe mental disorders, schizophrenia is most strongly associated with personal violence (Taylor et al, 1998). Comparisons of onset of violence and onset of psychosis suggest that almost invariably the illness comes first. Figures from the national confidential inquiry into suicide and homicide by people with men-

tal illness (Shaw et al, 1999) show that the common diagnoses of mentally ill people committing homicides are personality disorder, and alcohol and drug misuse. It is important at this point to differentiate antisocial personality disorder (APD), acquired sociopathy and psychopathy.

The *International Classification of Diseases* 10th edition (World Health Organization, 1992) describes APD as a disorder of the personality that usually comes to attention because of a gross disparity between behaviour and the prevailing social norms and is often preceded by conduct disorder in childhood. It also has to be accompanied by at least three of the following traits manifesting in late childhood or adolescence:

- Callous disregard or unconcern for others
- Irresponsibility and disregard for social norms
- Incapacity to maintain enduring relationships with others
- Low tolerance for frustration or low threshold for violence
- Inability to experience guilt or to learn from experience
- Tendency to blame or to rationalize aberrant behaviour to others.

Acquired sociopathy on the other hand is a term to characterize individuals who, following organic brain insult to brain areas such as the orbitofrontal cortex, present with symptoms of APD (Blair and Cipolotti, 2000).

The North American construct of psychopathy is a clinical construct traditionally defined by a constellation of interpersonal, affective, and lifestyle characteristics. Hare (1991) created a 20-item checklist (*Psychopathy Check List*; PCL), which goes into more detail about behavioural, affective and interpersonal characteristics. Higher scores on the PCL have been shown to predict relapse into crime in offenders. Two independent factors emerge from the PCL:

1. An emotional dysfunction factor largely defined by emotional shallowness and lack of guilt
2. An antisocial factor defined by antisocial behaviour.

High scores on the antisocial factor are more strongly associated with APD.

It should be noted, however, that there are difficulties in clearly delineating differences between neurobiology of violence in psychopathy and APD because of a degree of overlap in these two conditions and also because of inclusion of a range of subjects with varying diagnoses in studies carried out so far.

HOW RESEARCH INTO AETIOLOGY COULD HELP

Research into aetiology of violence in mental illness includes identifying the brain regions and circuits that may be involved in violence, with the hope that this knowledge may aid in clinical practice in risk management, prevention and treatment.

Emotion and violence

A neural circuit that includes several regions of the prefrontal cortex, the amygdala, hippocampus, hypothalamus, anterior cingulate cortex, insular cortex, ventral striatum and other interconnected structures, which are implicated in emotion regulation, also appears to be involved in violence (Davidson et al, 2000).

Insights from brain lesion studies

Individuals with damage to the frontal lobes (specifically the orbitofrontal and medial frontal areas) present with features of acquired sociopathy and violent behaviour (Blair and Cipolotti, 2000).

Clinical utility

The ability to predict which patients are likely to be violent in clinical practice has immense utility. A variety of clinical and actuarial tools are available to predict violence but none are sufficiently accurate. Biological measures that can predict violence are likely to complement present measures in violence risk prediction. The therapeutic methods available to treat the violent mentally ill are also not violence specific. A step towards development of biological treatments would be the identification of specific brain abnormalities that may underlie violence.

NEUROIMAGING INVESTIGATIONS INTO THE AETIOLOGY AND EFFECTS OF VIOLENCE IN THE MENTALLY ILL

Over the last 30 years we have moved away from X-ray and computed tomography (CT) to single photon emission tomography (SPET), positron emission tomography (PET), structural magnetic resonance imaging (MRI) and functional MRI (fMRI), which allow direct assessment of brain function as well as structure.

PET uses radioactively labelled tracer compounds injected into the body, which are detected externally using a gamma camera. Thus it is possible to monitor where the radioactive substances accumulate and where they are distributed. The tracer is used to reflect oxygen, blood flow and glucose uptake, and in doing so reveals a map of areas that are activated. Its

major benefit is its high temporal resolution that enables it to monitor change for periods up to a minute. Its spatial resolution, however, is relatively poor in comparison to MRI. The presence of radioactive substances mean that its uses have to be controlled to minimize exposure to radioactivity.

MRI produces images of the brain that look much like CT scans but that have an increased in-focus appearance and that have an ability to distinguish between white and gray matter. MRI uses a combination of powerful magnets, radiofrequency pulses and detection of electromagnetic energy to produce an image. The subject is placed in a strong magnetic field, which causes molecules that contain hydrogen (especially water) to line up, in a movement called precession. This essentially measures hydrogen nuclei densities, which are computed to produce images of the brain.

fMRI is an extension of the technology described for MRI and provides information on the brain function. It detects areas of brain activation as reflected by changes in oxygen concentration of the local blood flow. Changes in oxygen concentration in the haemoglobin results in the iron contained within the haemoglobin (deoxyhaemoglobin *vs* oxygenated haemoglobin) to highlight contrasting electromagnetic qualities, which this technique exploits to build up images of areas of brain activation. The benefits of MRI are its non-invasive nature, its high-resolution images and absence of radioactive exposure. However, the drawbacks include its poor temporal resolution (single time-point of activity is displayed) and the need for patient immobility during the scan itself.

THEORIES GUIDING NEUROIMAGING STUDIES

Evolutionary theory, psychodynamic factors, environmental conditions and a range of other theories have been explored into the roots of violence (Berkowitz, 1993). All major theories that dominate current research are described below.

Typology of violence and relation to neurobiological factors

Violence has been classified into categories such as reactive (response to frustration or threat) and instrumental (purposeful and goal directed), and also into similar categories such as impulsive (sudden, without planning) and premeditated (planned). This differentiation has been shown to have clinical utility and different neurobiological correlates. A study by Barratt et al (1997) showed that aggression is not homogenous even among antisocial persons, and that impulsive aggression is related to neuropsychological and cognitive psychophysiological measures of information processing beyond those factors related to criminality alone. Research also indicates that individuals with orbitofrontal damage are likely to show impulsive aggression whereas those with psychopathy tend to exhibit instrumental aggression (Cornell et al, 1996).

Somatic marker hypothesis

When an individual is faced with a threat a fight–flight response system is activated which involves the amygdala. In addition, the orbitofrontal cortex mediates the fight–flight response which is linked to the resultant autonomic response. According to Damasio et al (1990), defects in decision making reflect an inability to activate autonomic somatic states, both visceral and skeletal, linked to anticipation of punishment or reward following the given choice. The somatic marker hypothesis proposes that the activation of a somatic marker would lead to appraisal of future negative results, permitting deliberate selection of biologically advantageous responses, and trigger unconscious inhibition of response states by engagement of subcortical neurotransmitter systems linked to appetitive behaviour.

Prefrontal cortex and amygdalar dysfunction

Raine and colleagues in their studies (described below) theorize that brain areas of the prefrontal cortex (ventromedial and orbitofrontal areas) are linked to aggressive behaviour. The amygdala, a tiny structure located bilaterally in the forebrain, is one of the most crucial regions in the neural circuitry that processes emotion, more specifically negative emotions such as fear.

Violence inhibition mechanism

A model by Blair (1995) has implications for understanding violence in the context of mental illness. According to this model, most social animals possess a mechanism for the control of aggression – an aggressor terminates an attack when he/she notices cues of submission displayed by the victim. Blair (1995) proposed the existence of a functionally similar mechanism in humans, the violence inhibition mechanism, and that a deficit or a failure to develop this mechanism might under certain social conditions result in violent behaviour. The individual

without this mechanism could not inhibit aggression when the victim displayed distress cues. The ability to learn empathy during the developmental process is believed to be important in this mechanism.

NEUROIMAGING FINDINGS TO DATE

Table 1 describes the neuroimaging studies to date in mentally ill patients with a history of violence. Almost all studies have assessed males only. The findings, therefore, may not be applicable to females. Most studies have used PET, and a few have used SPET. There are only two studies that have examined brain structure and only one study each using MRS and fMRI.

Most PET studies have indicated (*Table 1*) decreased metabolism in the prefrontal cortex and medial temporal lobes. Specifically, Raine and colleagues (1994, 1997, 1998a,b) carried out a series of analysis on a group of murderers; apart from metabolic abnormalities they found that murderers with no early life psychosocial deprivation had more abnormalities compared to those with psychosocial abnormalities, and those with affective or impulsive violence showed more abnormalities than the predatory type. One of the SPET studies showed reduced blood flow in the prefrontal cortex and parts of the limbic system, which mediates emotion (Amen et al, 1996). The other study (Intrator et al, 1997) demonstrated increased blood flow in subcortical regions of psychopaths' brains during processing of emotional words.

Raine and colleagues (2000) examined prefrontal volumes by MRI in a group of APD subjects and found an 11% reduction in prefrontal grey matter volume in the absence of ostensible brain lesions. This is the first study that shows brain structure abnormalities in this group of APD. Another study (Laakso et al, 2001) showed lower posterior hippocampal volumes in a group of APD patients related to

TABLE 1.
Neuroimaging studies in patients with mental illness and violence

Modality	Study	Subjects (male/female)	Findings
PET	Volkow and Tancredi (1987)	Personality disorder (4/0)	Metabolic abnormalities in temporal lobe and frontal cortex
PET	Goyer et al (1994)	Personality disorder (12/5)	Inverse correlation between glucose metabolism in frontal cortex with history of aggression
PET	Raine et al (1994)	Mentally ill offenders (20/2)	Significantly lower glucose metabolism in both lateral and medial prefrontal cortex relative to controls
PET	Volkow et al (1995)	Personality disorder and schizophrenia (8/0)	Lower relative metabolic values in medial temporal and prefrontal cortex in than normal comparison subjects
SPECT	Amen et al (1996)	Personality disorder (30/10)	Decreased activity in the prefrontal cortex, increased activity in anteromedial portions of the frontal lobes, left-sided increased activity in basal ganglia and limbic system
SPECT	Intrator et al (1997)	Psychopaths (8/0)	Psychopaths differed from non-psychopaths in the pattern of relative cerebral blood flow during processing of emotional words
PET	Raine et al (1997)	Murderers (39/2)	Murderers were characterized by reduced glucose metabolism in the prefrontal cortex, while abnormal asymmetries of activity was also found in amygdala, thalamus and medial temporal lobe
PET	Wong et al (1997)	Schizophrenia/schizoaffective disorder (31/0)	Reduced glucose uptake noted at right and left anterior inferior temporal in non-repetitive offenders but only in left anterior inferior temporal in repetitive offenders
PET	Raine et al (1998a)	Murderers (39/2)	Those without history of psychosocial deprivation were significantly lower on prefrontal glucose metabolism than those with psychosocial deprivation and healthy controls
PET	Raine et al (1998b)	Murderers (39/2)	Affective (impulsive) murderers had lower prefrontal activity and higher subcortical activity than comparisons. Predatory murderers had activity levels similar to comparisons, but had excessive subcortical activity
Structural MRI	Raine et al (2000)	Antisocial personality disorder (21/0)	11% reduction in prefrontal gray matter volume
MRS	Critchley et al (2000)	Mild mental impairment (22/1)	Lower prefrontal concentration of N-acetyl aspartate (NAA), creatine phosphocreatine (Cr+PCr) and lower ratio of NAA/Cr+PCr in the amygdalo-hippocampal complex
fMRI	Schneider et al (2000)	Antisocial personality disorder (12/0)	Patients showed signal increases in cortical/subcortical areas during an aversive classical conditioning paradigm
Structural MRI	Laakso et al (2001)	Antisocial personality disorder and alcohol dependence (30/0)	Strong negative correlations between psychopathy scores and volume of posterior half of hippocampi bilaterally

fMRI = functional magnetic resonance imaging; MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopy; PET = positron emission tomography; SPECT = single photon emission computed tomography.

higher scores on the PCL as described by Hare. The first functional MRI study tested aversive conditioning in a group of APD patients with high scores on the PCL and a group of normal controls (Schneider et al, 2000). In the APD group, activity was increased than the control group in the amygdala and prefrontal cortex while making associations and this was interpreted as the APD group having to make greater efforts to learn associations because of deficits in emotional processing.

WHAT THE AVAILABLE STUDIES TELL US

Prefrontal cortex

Neuroimaging studies so far seem to confirm earlier ideas that prefrontal cortex functioning is abnormal in subjects who exhibit violence. Two areas of the prefrontal cortex, the orbitofrontal cortex and ventromedial cortex, appear important in this regard. This involvement of the prefrontal cortex can be understood if we consider the function that this area serves. It plays a key part in fear conditioning and stress responsivity, is involved in regulation of arousal, and damage to this part leads to impaired planning, deficient impulse control and anticipation.

Psychopaths display behaviours that are characterized by deficient inhibition, and lack of self-control and planning. It is important, however, to distinguish between orbitofrontal or ventromedial prefrontal cortical function which is linked to impulsive aggression, whereas dorsolateral prefrontal dysfunction has been linked to executive dysfunction in violent offenders (Gorenstein, 1982).

Amygdala

The amygdala plays a key role in processing emotion and mediating fear. According to Blair (1995) amygdala dysfunction could explain lack of fear and empathy in psychopaths. Conditioning studies indicate abnormal patterns of brain activation in the amygdala and parts of the limbic system.

Reciprocal connections

Abnormalities in the prefrontal cortex and the amygdala could be linked. Research findings indicate that the mechanism underlying suppression of negative emotion is via an inhibitory connection from regions of the prefrontal cortex to the amygdala (Davidson et al, 2000). Thus, the prefrontal cortex normally inhibits the amygdala and damage to the prefrontal cortex releases this inhibition. This functional relationship between the prefrontal cortex and amygdala may be the result of a reciprocal relation in glucose metabolism between these two areas.

PITFALLS IN RESEARCH

Although these new neuroimaging techniques have led to interesting studies the methodological problems in the studies cannot be ignored. Most of the studies have not carried out assessments for levels of psychopathic traits and include a diverse range of psychiatric conditions (like schizophrenia, alcohol dependence, personality disorder and mental impairment) with violence as a common factor. It is thus not known how the effects of these disorders on the brain confound the results. Studies have examined predominantly male subjects and used isolated measures of brain functioning. The definition and type of violence in some studies is not clear, especially because the subtypes of impulsive and premeditated violence seem to have different biological determinants.

In addition to the above noted methodological limitations of the research, there are some fundamental theoretical questions that need to be addressed before neuroimaging research findings can become clinically relevant. The most important is whether we can ever really localize violent behaviour or the propensity thereof to a few brain areas or brain circuits. Are such efforts fruitless? Violent behaviour occurs in a range of psychiatric conditions, as discussed. There may be problems with the assumption that biological determinants of violence in all psychiatric conditions are similar.

FUTURE DIRECTIONS AND CONCLUSIONS

Initial studies have brought important insights into brain areas involved in violent behaviour, indicating involvement of the prefrontal cortex and areas of the limbic system such as the amygdala. In future studies an integrative rather than a reductionistic approach is required which could be achieved by multimodal assessments (e.g. structure and function by neuroimaging, information processing and cognitive abnormalities by neuropsychology and electrophysiology) of a variety of populations implicated in aggression and violence. HM

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KEY POINTS

- Mentally ill people have higher rates of physical violence than the general population, mainly towards people who have close contacts with them.
- Violence can affect clinical management and public perception of people with mental disorders.
- Neuroimaging techniques have revealed abnormalities in the prefrontal cortex and amygdala in association with violence.
- Neuroimaging studies may allow to predict violent behaviour in mentally ill individuals and to identify anomalies in brain functioning that may be amenable to treatment.
- Neuroimaging studies exploring the aetiology of violence in mental disorders, however, are scarce and subject to methodological and theoretical limitations.