

Imaging and Genetics: *Future Applications in the Emergency Room*

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ABSTRACT

Developments in brain imaging and genetics are revolutionizing our understanding of behavior, particularly the role of neurobiology in aggression and violence. In the emergency room (ER), these developments will have special application for the evaluation of patients who are assaultive and potentially homicidal. Though useful, traditional psychiatric diagnosis with its focus on categoric conditions such as personality disorders, schizophrenia, and delusional states does not tell the whole story. Brain images have shown the role of structural and functional disturbances, particularly of the prefrontal cortex and limbic system in the emergence of violent behavior. Similarly, discoveries such as the presence of an aberrant gene for producing monoamine oxidase A, which interacts with the environment to prompt antisocial behavior in boys, are making significant contributions to our understanding of how genetic abnormalities affect human behavior, particularly aggression and violence. These developments will inevitably influence not only how aggression is diagnosed in the ER, but also the disposition of afflicted individuals.

INTRODUCTION

The diagnosis of violent behavior in the emergency room (ER) has become increasingly complex the past 15 or so years because of the extraordinary developments in genetics and neuroscience. Prior to chromosomal studies and brain imaging, psychiatrists could only rely reasonably on the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition-Text Revision,¹ Axis I diagnoses for establishing whether violent patients had a disease or whether they should be seen

FOCUS POINTS

- Brain imaging and genetics are important in assessing violence.
- Technologic developments will increasingly allow application of neuroscience and genetic findings in the emergency room.
- Brain imaging has revealed many correlations of brain structure and function with violent behavior.
- Studies of genes have shown associations between individual and multiple gene abnormalities and violence.

informally (at least since the ER is not a court of law) as responsible for the violent acts they committed—acts which caused injury or death to others and/or damage to property.

Traditional psychiatric diagnoses, such as paranoid schizophrenia, delusional disorder, and bipolarity, have been very useful in parsing out clearly disturbed violent patients. Many of these disorders, particularly paranoid delusions, have a statistically significant correlation with violence. On the other hand, the studies are mixed on the broader question of whether psychiatric patients generally are more violent than the general population. Patients in a manic phase may be so deranged that they are capable of hurting another person, perhaps not out of intent but more out of unfettered energy and disordered thinking. However, much empirical research has shown that among incarcerated populations, mental illness seems higher than in the general population. Studies^{2,3} have shown that well over 20% of incarcerated defendants who are evaluated for competency are found to be medically and legally lacking competency to stand trial.

Separate from the serious psychotic disorders that are represented in conventional psychiatry and that have features of uncontrollability, there is a growing literature of many who have biologic disturbances that can cause violence.^{4,5} These new

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discoveries are becoming transformative in our conception of violence. We are beginning to debunk some Freudian notions that have been held for years in our understanding of suicide and violence to third parties. One of the most significant of these is that all of us given the right situation are capable of violence, be it self or other inflicted. Freudians have long held that all of us have the extremes in us—the evil of Hitler and the potential good of caring figures like Mother Teresa. However, recent data is clearly calling this into question. We are not all capable of violence against self or others. The brain has limits which may be specific to people; emotions seem to be on a rheostat and many of us do not reach a level of anger or desperation to trigger a violent response. Perhaps by genetics or environment through learning, most of us find alternative pathways for handling anger and frustration. This capacity is biologic. Not everyone can control anger when it reaches a certain level.

At the same time that we are discovering that not everyone is capable of violent acts, those in the population who are capable of killing themselves or others have been increasingly found to have specific neurophysiology, including anatomic and biogenetic characteristics, that distinguish them from the rest of the population. This article briefly explores some of the findings of brain imaging and genetics, which strongly point to neuron-biology as an important cause of violence. The focus is on the potential future relevance of biologic information obtained from these technologies regarding violence in the emergency diagnosis and treatment context.

BRAIN IMAGING AND VIOLENCE

The case of Phineas P. Gage in the 19th Century shifted focus to the frontal lobe, especially the prefrontal cortex (PFC), as a significant source of violence and aggression. In this case a railroad foreman, while attempting to split rock with dynamite, experienced an iron bar blasting through the front of his skull. This caused serious damage to his PFC, resulting in major personality changes of an antisocial nature.⁶ Since this event there has been considerable focus on the relationship between violence and damage to the frontal and particularly PFC as well as parts of the temporal and parietal lobes. There have been several studies⁷ over the past 15 years demonstrating that a significant relationship exists between head injuries and violence.

Three basic biophysiological syndromes seem to be associated with impairments that may lead to violence. The first involves defects of the frontal lobe, most particularly the PFC, which implicates higher cognitive functions, such as consciousness and abstractions, and which could facilitate violent occurrences because it results in an afflicted person being unable to shape or comprehend concepts of right and wrong or to appraise the consequences of violent acts. The PFC participates in inhibiting outbursts of rage and

aggression. The second syndrome involves abnormalities of the limbic area of the brain, including the medial temporal cortex and the amygdala, which is responsible for the generation of affect and emotions. Abnormalities could result in the elicitation of feelings that arise independent of provoking circumstances. In such circumstances the patient will tend to show random outbursts of violence and an inability to control impulses. Finally there may also be abnormalities, whether genetic or developmental, in the association areas of the brain, which could lead to distortions in perception. These areas include the PFC, especially its anterior segment, which, along with the parietal association cortex, is involved in “attention association.” The PFC, which is important for managing bodily movements and complex behaviors, is also connected to other association cortices, most particular the parietal-temporal-association area, and the limbic (medial side) cortex. When disturbances occur in the association areas, aggression and violence may be induced by innocuous behaviors, such as waving at a person, which could easily be misperceived as threatening.

Brain imaging studies of the frontal lobe are contributing to our understanding of the neural basis of antisocial behavior. Raine and Yang⁸ conducted some of the most important research on antisocial personality. In the early 90s using positron emission tomography (PET) scans, Raine and colleagues^{9,10} studied 41 alleged murderers who had pleaded not guilty by reason of insanity and compared them with age- and sex-matched controls. He showed that murderers compared with normal controls have reduced prefrontal glucose metabolism. In a later study of 41 people charged with homicide who pleaded “not guilty,” Raine and colleagues¹¹ divided the group into those with and without a history of social deprivation. They discovered that the alleged murderers who had a relatively normal upbringing showed lower prefrontal glucose metabolism compared with those who experienced deprivation and a control group. They concluded that murderers are strongly influenced by prefrontal deficits even in the absence of a “social push” from a deprived environment. A subsequent study¹² with the use of single photon emission computerized tomography (SPECT) demonstrated a correlation between aggressive, antisocial behaviors and reduced blood flow in the frontal lobe. In this study, 21 violent offenders unrelated to substance abuse, psychosis, or medication were scanned and shown to have decrease fronto-temporal perfusion.

Finally, with regards to the frontal lobes, particularly the PFC, there have been magnetic resonance imaging (MRI) studies¹³ of structural differences in the brains of individuals with antisocial and psychopathic personalities. Raine and colleagues^{14,15} found marked reduction, as much as 11%, in the gray matter of the PFC of patients with antisocial personality disorder. They speculated that this decrease might be related to diminished qualities of the subject, such as lack

of conscience, low arousal, and inadequate fear conditioning—features which when normal would likely inhibit him or her from committing bad acts. Similar findings have been shown in children diagnosed with conduct disorder. One small study¹⁶ of 10 youths with early onset conduct disorder compared to 10 healthy controls found as much as a 16% reduction in the gray volume of PFC (and temporal lobe cortex) in the afflicted children.

More recent research¹⁷ regarding the PFC and violence points to the fact that brain abnormalities associated with antisocial personality disorders may be centered primarily in two particular prefrontal regions, the orbitofrontal cortex, which along with the anterior cingulate cortex plays an inhibitory role on aggression, and the dorsolateral cortex. Research⁸ has shown that lesions of the orbitofrontal region of the PFC manifest themselves in afflicted individuals by impulsivity, disinhibition, and disregard of the consequences of actions, symptoms not unlike those that Gage exhibited after he sustained injury to his PFC. PET studies¹⁸ have been conducted on six impulsive epileptic children who were also aggressive and have been compared to seven non-aggressive epileptic children and 17 normal adults. The researchers found reduction in glucose metabolism of the orbitofrontal cortex as well as the medial PFC (and the temporal neocortex) in the aggressive epileptic children. Functional MRI (fMRI) studies¹⁹ of conduct disorder patients have revealed dysfunction in the orbitofrontal cortex related to motivation and reward. Structural as well as fMRI studies of the orbitofrontal cortex have resulted in similar findings seen with the PFC by showing, respectively, reduction in the volume of gray matter^{20,21} and activation during tasks involving fear conditioning.²²

Dysfunction of the dorsolateral PFC has also been shown to be associated with aggression and violence. For the most part, damage to this section of the PFC results in difficulties with attention, most particularly shifting attention, as well as problems with planning and general decision making. Studies¹⁸ have shown reduced metabolism in this region of the brain in individuals manifesting aggressive behavior. A SPECT study²³ of 10 dementia patients with and without aggression revealed hypoperfusion in the patients with aggression, not only in the dorsofrontal area but also the left anterior temporal and right parietal cortices as well.

Disturbances of the temporal lobe have also been implicated as a cause of violent behavior. Similar to the frontal lobe, studies^{16,24} have shown correlations between reduced temporal lobe volume and conduct disorders as well as psychopathic behavior. PET studies²⁵ have shown reduced temporal lobe metabolism and blood flow in recidivistic violent men. Some of the men studied demonstrated decrease functioning in their frontal lobes. When this occurred the subjects were unable to shape a moral response. A later study²⁶ using fMRI showed reduced function of the temporal cortex in violent offenders

compared with controls. A SPECT study²⁷ of patients with antisocial personality disorder revealed decreased blood flow in the right middle temporal gyrus. Metabolic reductions as discovered through PET have also been found in the medial temporal cortex in psychiatric patients who engage in repetitive violent acts.²⁸

The amygdala, located in the temporal lobe, has been shown to be associated with aggression and violence. Studies²⁹ have found a high rate of atrophy, as much as 20%, of the amygdala in aggressive and violent patients. Imaging studies^{9,10} have also shown abnormalities in amygdala functioning, including decreased activation of the amygdala during affective stimuli in psychopaths and in adolescents with conduct disorders.^{30,31} Since the amygdala is involved with conditioned-fear responses, there has been much attention focused on the diminished fear responses and empathy of psychopaths. In an experiment²² to study the responses of the amygdala to faces associated with a painful shock, normal volunteers were found to have increased activity in their amygdalae. This reaction among normal subjects is compatible with current ideas of the function of the human amygdala, which is to modulate vigilance levels and facilitate the processing of memories of material that is emotionally arousing. Hence, fearful or threatening faces activate the amygdala³²; psychopaths, in contrast, demonstrated essentially no change in activity in their amygdalas.

Similar findings³³ emerged from research on 17 boys—compared to 13 normal controls—with conduct problems who manifested high levels of callous-unemotional traits. With the use of fMRI the researchers found significant reduction in amygdalar activity on the right side to fearful faces. These results found in unemotional children as well as psychopaths are consistent with studies³⁴⁻³⁷ that show an inverse correlation between amygdala activity and elevated scores in the Psychopathy Personality Inventory. Some³⁸ speculate that in psychopaths, the pathway between the amygdala and PFC is disrupted, thus resulting in the minimization of human emotions that are essential for personal control, eg, regret, guilt, and fear.

In addition to the frontal and temporal lobes, the parietal lobe, which is involved primarily in integrating sensory data from various parts of the body and thereby has an associative function, has been found to manifest reduced metabolism, particularly in the superior parietal cortex in aggression and violence. PET studies^{9,10,39} have shown reduced metabolism in the superior parietal cortex in patients who are aggressive and those with impulsive personality disorders. Studies^{20,40} of murderers have shown decreases in glucose metabolism in parts of the parietal lobe. Two other brain areas that demonstrate functional impairments in criminal psychopaths through fMRI are the anterior and posterior cingulate cortices.

Regarding the anterior cingulate cortex, a recent study⁴¹

using SPECT scans of 11 young males convicted of impulsive murders compared their brain functions with a healthy control population. The researchers discovered lower cerebral blood flow in the murderers in brain regions involved with impulse control, such as the anterior cingulate and orbital cortices. These regions are essential for managing anger and are basic to self-censorship, evaluation of future consequences of behavior, and basic inhibition.

A last note on brain imaging and violence was a recent study²¹ of violent offenders compared to nonviolent men conducted in Finland that showed significant differences in the brain structure of these groups. This study involved 26 chronically violent men and 25 nonviolent controls. The researchers found that violent offenders had larger volumes of white matter bilaterally in the parietal and occipital lobes as well as in the left cerebellum. The right cerebellum, in contrast, had larger volume of gray matter. Researchers also found areas of atrophy in the orbitofrontal and frontopolar cortices as well as the postcentral gyri in offenders. Psychopaths showed conspicuous changes in these areas, suggesting to the researchers that aberrant neurodevelopment may be related to early onset aggression and antisocial behavior.

In effect, research is supporting the notion that repetitive acts of aggression are grounded in a neurobiologic susceptibility. As pointed out by Siever,⁴² several processes induce aggressive acts, which support a neurobiologic vulnerability. In many there is a failure of the PFC to modulate aggressive and violent acts. There is also an imbalance operating between prefrontal inhibitory influences and hyper-responsivity of the amygdala and other parts of the limbic system. Furthermore, as shown in the next section, there are biologic problems associated with violence such as insufficient serotonergic facilitation, excessive catecholaminergic stimulation, and imbalances of agents in the subcortical region, to name a few.

GENETICS AND VIOLENCE

There have been studies of biochemical changes associated with violent crimes that directly or indirectly reflect brain abnormalities and genetic dysfunction. Research has shown a relationship between violent crimes and low cholesterol⁴³; elevated levels of L-tryptophan plasma and violence^{44,45}; and low levels of serotonin, depression, and violence, which can be manifested as either suicide or homicide.⁴⁶ An association has also been established between violence and levels of catechol O-methyltransferase (COMT).⁴⁷

Regarding the latter, a study⁴⁸⁻⁵¹ was conducted involving 240 children with attention-deficit/hyperactivity disorder who were evaluated for signs and symptoms of conduct disorder. Genetic testing was performed to establish whether a particular variant of the COMT gene was present in these children. The researchers discovered one variant of that gene

in which valine is substituted for methionine in one section of the gene. Children with two valine variants of the gene performed worse than children with either two methionine variants or methionine/valine combinations on tasks assessing prefrontal cortical activity. The researchers concluded that the two valine variant gene is associated with children manifesting antisocial behavior. When inadequate, prefrontal cortical functioning, which is an essential component in the inhibitory system, is correlated with antisocial conduct.

A study⁵² conducted several years ago has been particularly important in establishing a relationship between a gene for enzyme production and violent behavior. This study, stimulated by an observation in 1993 of a Dutch family exhibiting a defect in this gene demonstrating violent behavior, involved a large group of boys who were followed from birth to adulthood. The purpose of the study was to determine what factors might explain why some abused children become violent later on in adolescence and adulthood.⁵³ This study established that there is a gene that codes for monoamine oxidase A (MAO-A), an enzyme that metabolizes neurotransmitters in the brain. Some children are born with a defective MAO-A gene, which contains a short allele thereby resulting in lower production of the MAO-A enzyme. When this occurs neurotransmitters such as serotonin, norepinephrine, and dopamine are not effectively metabolized, which sets the stage for the development of violent men. The presence of the defective gene in itself does not lead to violence; however, if there is abuse during the childhood of the afflicted male the chances of producing a violent and sociopathic male can increase to as much as 85%.⁵³ Male children with this genetic abnormality who do not experience abuse are as likely as a normal child to become violent. Since this gene is X-linked, normal girls with two Xs are most unlikely to experience reduction in MAO-A.

A recent study⁵⁴ has made an important biologic linkage among familial adversity, particularly childhood abuse, changes in brain physiology, and violent behavior as seen with children with low MAO-A enzyme production. Hence, epigenetic regulation through environmental assaults (ie, child abuse) has been shown to be specifically associated with decreases of glucocorticoid receptors in the hippocampus and increased hypothalamic-pituitary-adrenal function activity that augment the risk of suicide and likely other forms of violence.

The MAO-A study⁵⁵ has been replicated many times. Most recently a study⁵⁶ was conducted in which 2,500 men were questioned about the violent acts they had committed. Based on the survey, the researchers identified men who carried a rare low-activity variant (2R) of the MAO-A gene. Men with this 2R variant were found to engage in a level of violent behavior during adolescence, which was nearly twice as high as those with other variants.

Studies⁵⁷ have also been conducted to determine how the low-activity (L) variant of the gene that codes for MAO-A

affects brain structure to increase the risk for aggression and violence. Perhaps the principle way it directly affects parts of the brain is through the high production of serotonin that develops from the reduced presence of the MAO-A enzyme. This elevated serotonin level is “toxic” in that it induces the brain to compensate and thereby results in brain alterations, which make those affected more susceptible to violence. Using MRI, Meyer-Lindenberg and colleagues⁵⁷ studied the difference in brain structure between people with the H (high) variant of the gene for MAO-A and those with the L variant. The researchers found that males with the L variant had an 8% reduction of gray matter in both the cingulate cortex and the amygdala, which is related to the regulation of mood, and a 14% increase in volume of the orbitalfrontal cortex, which is important for impulse control and motivation. The increase volume of the orbitalfrontal cortex reflects, according to the researchers, deficient pruning of neurons, which is believed to be developmental and responsible for impaired function of that part of the PFC. The researchers reflect that alone this genetic aberration does not explain violence; however, it most likely contributes to violent proneness in combination with other influences of a genetic and psychosocial nature.

Genetic research on violence is expanding in many directions. Two additional studies^{58,59} of other genes deserve to be mentioned in this regard. The first⁵⁸ studied two genes that affect the way the brain uses the neurotransmitter dopamine, which is associated with motivation and pleasure, but which when working in tandem increases the risk of childhood conduct disorder and adult antisocial behavior. This study involved following 872 males participating in a National Longitudinal Study of Adolescent Health. Data, which consisted of questions regarding conduct disorder behavior, were collected when the participants were ages 11 and 19 years, then 2 years later, and finally again when they were between 18–27 years of age. DNA samples were also taken to determine if they had variants of the two genes of focus in the study. Regarding the first of these genes, the DRD2 gene, the carriers of one variant, the A-1 allele, have fewer dopamine-2 receptors in the brain, less dopamine activity than normal in the central nervous system, and reduced brain glucose metabolism. The researchers suspected that this gene is involved in a condition referred to as reward deficiency syndrome, where a person requires thrill-seeking behavior to compensate for the insufficient biologic rewards that he is getting from behaviors that would normally provide such reward. The second gene, the DRD4 gene, is involved with motivation, attention, and exploration, and, therefore, is thought to be responsible for stimulating cognitive faculties and expressing emotions. The 7 repeat allele variant of this gene is associated with psychological problems. Alone, neither of these gene aberrations has been shown to affect conduct disorder or antisocial behavior, but together they interact to produce these antisocial conditions.

The second study⁵⁹ involved a variant of a gene that affects androgen activity. The androgen receptor gene codes for a protein that facilitates cells to respond to androgen. One segment of this gene is the CAG segment which has been shown to affect androgen activity; a short region of repeating of the CAG segment seems related to increase androgen activity and criminal behavior. The study of 26 persistently violent men showed that murderers and rapists had shorter CAG repeats than normal subjects, and those who had been convicted of both rape and murder had even shorter CAG repeats than those convicted of one of these crimes alone.

Finally, the last gene that needs to be mentioned was discovered in a study⁶⁰ at the National Institutes of Health in 2002. A single gene was located, which has been shown to affect a person's response to emotionally charged stimuli, like an angry face. This gene encodes the production of a protein that transports serotonin back into the neurons from the synapse, thereby minimizing the effect of serotonin on surrounding neurons. There are two structural alleles of the transporter protein gene, one of which has a short promoter region and therefore produces less of the transporter protein. This allows serotonin to remain longer in the synapse and, therefore, extends its influence on the neurons. Using fMRI the researchers discovered that individuals with the short allele producing less transporter protein showed greater activation of their amygdalae. Hence, someone with a less transporter protein will react more to stimuli, like angry faces, which would likely induce violent responses.

CONCLUSION: THE RELEVANCE OF BRAIN IMAGING AND GENETICS IN THE EMERGENCY ROOM

The future of emergency diagnosis and treatment will be inevitably changed by virtue of new technologies. Resort to psychiatric diagnosis alone for determining the causes of aggressive behavior will be superseded by focus on neuron-biology through advances in brain imaging and genetics. The human genome has been delineated and in the near future individual genomes will likely be available to assist the doctor in more precise diagnoses of aggressive and violent behaviors and in selecting treatments on an individual basis that will maximize therapeutic benefits and minimize adverse outcomes. In keeping with this development, sometime in the future cord bloods will be taken routinely from birth and used to delineate the individual's DNA so that genetic information will be readily available under emergency conditions to assure proper assessment of violent people. Hence, a patient presenting with an episode of violence and a history to support that will have their DNA contrasted with norms to determine if they have a predisposition to aggression and violence, such as would be seen with an aberrant MAO-A gene.

The study⁵⁸ involving the interaction of two genes, the DRD2 and DRD4 genes, might turn out to be the prevailing pattern for the majority of findings implicating genetics and violence. Behavior is so complex that finding one gene that can explain the cause of violence, such as with the MAO-A abnormalities, will probably happen infrequently. However, with sophisticated mathematical models and the use of the computer, interactions among genes will be shown most helpful in setting a framework for mapping out the role of genetics in aggression and violence.

Similarly, imaging technologies will undergo further development—such as altering size to enhance portability—and become more accessible for immediate use. MRIs and PET/SPECT scanning may one day be standard practice in the ER. Furthermore, the technical and statistical problems now a point of controversy with imaging technologies will be resolved. Efforts have been underway through programs such as the National Institutes of Health initiative's Biomedical Informatics Research Network to standardize the hardware of technologies, particularly MRI and fMRI, and to improve their reliability and reproducibility in research as well as practice.⁶¹ Information provided for comparing the images of violent individuals to normative scans will be enhanced both in scope and precision.⁶² **PP**

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