

The Neuropsychopharmacology of Criminality and Aggression

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Although the idea that aggression has biological components is not a new one, recent research in genetics, neuropsychopharmacology, and neuroimaging has helped clarify the biological contributions to aggression. Studies to date have focused on serotonergic function and impulsive aggression. Reduced levels of cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) are associated with impulsive aggression. Pharmacochallenge studies have found decreased serotonergic responsiveness associated with impulsive aggression. Neuroimaging studies suggest a role for the prefrontal cortex, along with other regions of the brain, in the expression of aggression. Serotonin is not the only aspect of brain function implicated in impulsive aggression, and further work is being done on other neurotransmitters and neuropeptides.

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The notion that the expression of aggression may be related to brain function is not a new one. From the Hellenic civilization comes the Homeric tale about the family of Orestes and Agamemnon, who carried on their forefathers' tendencies toward crime and murder. From their ancestor, who attempted to deceive the gods, "the curse descended . . . in the form of what the Greeks called *ate*, a strong if not actually irresistible impulse to crime" (1). While this tale may not have been specifically about our current concept of genetic heritability or the passage of a biological predisposition to aggression, it may have spoken to the story of a family seemingly destined to suffer the effects of violence from generation to generation.

Defining the relation between the brain and violent aggressive behavior has been a challenge, given the limitations of science in comparison with the complexity of human behavior. The philosophical connotations of early case studies such as that of Phineas Gage, the questionable validity of early psychosurgical studies, and questions about ethical research contributed to early skepticism about the validity of the associations made between brain abnormalities and aggressive behavior, as well as to an apprehension of the possible social consequences of hasty scientific conclusions. Reservations continue: As stated in a recent critical review, "Tentative findings cautiously reported in the technical literature are often oversimplified in the clinical scientific or lay media and in

communications with governmental policy-makers" (2). Concerns like this have led to important and appropriate changes in the way experimental studies have been carried out in animal and human subjects, as well as an increased awareness of the need to study aggression and criminality in context by integrating biological studies with other scientific disciplines.

This paper provides a review and update of biological studies in aggression, with a special emphasis on the neuropsychopharmacology of impulsive aggression. Some of the clinical and forensic ramifications of the findings will be discussed. There is considerable overlap between criminal behavior and aggressive behavior, but there are significant differences. Crime is a legal concept. It is represented in the DSM-IV under the V code of "adult antisocial behaviour" and, in combination with other behaviours, under "antisocial personality disorder" and "intermittent explosive disorder." While certain psychiatric conditions are associated with increased criminality and an increased risk of committing a crime, no current DSM-IV diagnosis uses the committing of a crime as the sole criterion. The presence or absence of a medical or psychiatric disorder does not categorically define the behavior of a person as criminal or noncriminal, just as a criminal act does not necessarily reflect underlying psychopathology.

Criminal acts can be classified as violent versus nonviolent and premeditated versus nonpremeditated. Violent crimes against persons include homicide, attempted homicide, physical assault, and sexual assault. Nonviolent crimes are usually crimes involving property, such as theft, vandalism, and the breaking of civic laws. Nonpremeditated crimes do not involve the same kind of forethought as do premeditated crimes. Although nonpremeditated crimes may not result in

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gain for the perpetrator, they can be committed by persons who know the difference between right and wrong, or legal and illegal acts.

A significant subset of nonpremeditated crimes involve impulsivity. Still, it is important not to confuse impulsivity, a psychiatric term, with nonpremeditation, a legal one. Impulsive acts of aggression may share such similarities with nonpremeditated crime as a significant relation to environmental triggers. The legal and moral implications of impulsive behaviour can not be defined by psychiatry. Important distinctions in psychiatric categories may not have forensic relevance. For example, impulsivity could be a major factor in both premeditated and nonpremeditated crimes. The extent to which impulsivity may affect the status of a person's free will and ability to know right from wrong is beyond the scope of this paper, but at this time impulsivity is not considered either in law or psychiatry to be the kind of "profound mental disturbance" (3) that affects one's ability to know the difference between right and wrong or reality and fantasy.

Impulsivity is an aspect of personality. Personality is divided into 2 major components: temperament and character. Temperament is considered to be heritable, recognizable in early life, relatively stable, and correlated with a variety of biological variables. That aspect of a person related to relationships with others and with society and the set of values the person applies to these relationships is considered to be character, which is less influenced by biological factors than is temperament.

The biological contribution to criminality, in particular violent criminality, has been most studied in relation to impulsive aggression. Impulsive aggression is a construct that has been useful as a way of looking at a subset of impulsive and aggressive behaviours in animals and humans. Although it needs further investigation, there is evidence that the construct has validity and can be separated from aggressiveness in general (4).

In some individuals, aggression is a stable characteristic. Work focusing on aggression in delinquent youths has found that aggressiveness and delinquent behaviour are associated with each other and that their relation continues over several decades in a significant proportion of cases (5). In boys with a diagnosis of conduct disorder (CD), one study, although not focused on aggression, showed that 87.7% of the young male subjects continued to qualify for the diagnosis over a period of 3 years, based on continuing problems with criminality (6). Thus, in some individuals, the early appearance of CD may be linked to ongoing criminality and aggression.

Patterns of criminality can be associated with measures of temperament, as opposed to a past history of criminal behaviour. This is illustrated by a study showing that Psychopathy

Checklist-Revised (PCL-R) scores were the best predictor of recidivism of violent crime: measurements of personality—not simply a past history of criminality—were predictors of violent crime. Seventy-one juvenile delinquents were released and followed up by a review of criminal records. The recidivism rate during the follow-up period was nearly 80%. In this study PCL-R scores, modified to exclude histories of previous crime, were not correlated with time at risk, recidivism overall, or number of nonviolent offenses. PCL-R scores, however, were correlated with the number of violent offenses committed in the follow-up period ($r = 0.26$) (7). A tendency toward psychopathy may be more correlated with relatively stable aspects of personality than with a history of a criminal act. The multitude of studies looking at the relation between criminality and aggression, and the high rate of recidivism of both, help to show that these behaviours are related to underlying temperaments. They do not speak to the cause of the behaviour, nor do they delineate biological, genetic, or environmental influences. The rest of this paper will review these aspects of criminality and related behaviours. We will review data relevant to genetics, neurotransmitter activity, and brain function as assessed by neuroimaging.

Genetic Studies

Behavioural genetic studies determine the lower limit of biological contribution to temperament and behaviour. Genes can not account for all of the biological contribution to behaviour, nor can they dictate the interaction between the environment, the brain, and personality. Even so, studies to date have found some aspects of aggression and criminality to be significantly heritable. Among genetic studies, the 3 relevant kinds are twin studies, adoption studies, and polymorphism studies.

Twin studies measure the degree of concordance between monozygotic and dizygotic siblings on specified traits and seek to establish whether genetic heritage plays a role in expression. To date, there have been 4 twin studies looking at criminality as a single variable. In 3 of the studies, a statistically significant difference in concordance between monozygotic and dizygotic twins was found for criminality (8–10), while the fourth study found only a trend in concordance for criminality (11).

A study of monozygotic twins raised apart from an early age found that the number of symptoms of an antisocial personality disorder (DSM-III) showed a heritability estimated at 0.42 for CD symptoms and 0.29 for adult symptoms of an antisocial personality disorder (12). In one of the few twin studies to differentiate between types of aggression (as opposed to criminality in general) in a population of male twin pairs, heritability of 47% was found for direct physical aggression, 40% for indirect physical aggression, and 28% for verbal aggression (13). Direct physical aggression was defined as violence toward others, indirect aggression was defined as

aggression toward objects, and verbal aggression was defined as aggression expressed with the voice.

Adoption studies can further describe the relative contributions of environment and genetic heredity to criminality and aggression. In adoption studies, a 4-cell study design is used to evaluate the relative contributions of environment and genetics. Aggressive behaviour in adoptees is associated with the same behaviour in the biological parents: if an association is found, a genetic effect is implied. If a positive correlation is found between the adoptee's behaviour and the rearing family, an environmental effect is implied. A study of 14 427 nonfamilial adoptions in Denmark found a significant relation between the number of convictions among the biological parents, particularly fathers, and the rate of convictions among adopted-away sons (14). A similar relation was seen when chronic offending in parents was examined separately. In this study, however, only property of offending (as opposed to violent offending) had a significant relation. Other adoption studies have found similar results. Bohman found that petty criminality was heritable if the child and biological parent were not alcohol abusers (15). If the child or biological parent had both criminality and alcoholism, the criminality was attributable to alcoholism. This study, in which the number of subjects was small, also failed to find a significant relation with violent criminality.

Evidence for abnormalities at the gene level that could transmit traits of increased aggression has been somewhat confusing. The most-studied DNA polymorphism is within the noncoding region of the tryptophan hydroxylase (*TPH*) gene. *TPH* is the rate-limiting enzyme in the synthesis of serotonin (5-HT), putatively involved in the expression and regulation of impulsive aggression. Nielson and others (16) reported that impulsive violent offenders with 1 or 2 copies of the *TPH* *L allele had significantly lower cerebrospinal fluid (CSF) concentrations of CSF 5-hydroxyindoleacetic acid (5-HIAA) when compared with impulsive violent offenders with 2 copies of the *U allele. The *L allele in impulsive and nonimpulsive violent offenders was associated with a greater frequency of past suicide attempt (*LL: 65% vs. *LU: 53% vs. *UU: 17%, $P < 0.02$). In fact, almost all of the offenders who attempted suicide had either the *LL or *UL genotype, independent of CSF 5-HIAA levels. *TPH* genotype was not associated with such psychiatric diagnosis as affective or anxiety disorders. Although Nielsen and others (17) replicated the finding in a study of 804 Finnish alcoholic offenders, and there has been an independent replication by New (18), it should be noted that there have been nonreplicating studies published (19–21) which either correlate the more common *U allele with suicidality or aggression or do not find a correlation (Coccaro, unpublished data). That these studies fail to replicate the original findings may be related to the fact that the polymorphism is on the noncoding region of the *TPH* gene. Hence, it may be in linkage disequilibrium with an

unknown polymorphism in some study populations, but not in others (22). An association between antisocial alcoholism and the *C allele biallelic polymorphism of the 5-HT_{1D} receptor has been found (23). Antisocial alcoholism is defined as alcohol abuse along with antisocial personality disorder or intermittent explosive disorder. Violence in people with schizophrenia has been associated by Strous (24), with replication by Lachman (25), with a “low activity” allele of a biallelic polymorphism for catechol-o-methyltransferase (COMT).

Although more research is needed to clarify inconsistent results, it is estimated that about 40% of the propensity toward antisocial behaviour may be attributable to heredity (26). A significant part of this could be related specifically to violent impulsive behaviour. Genetic studies have not yet located that part of the genetic code responsible for these differences, but they do provide the theoretical groundwork for the further study of the neurobiology of aggression, as is discussed in the next section.

Serotonin

In 1976, Åsperg and others found that reduced levels of CSF 5-HIAA in patients with depression were associated with a history of suicide attempts (27). Of the patients with the lowest 5-HIAA levels (who also had histories of more violent suicide attempts), 2 completed suicide at a later date. The possibility that decreased levels of a neurotransmitter metabolite could lead to more impulsive violent behaviour was replicated and extended to aggressive behaviour in general by Brown and others (28), who found a trivariate relationship between aggression, history of suicidal behaviour, and CSF 5-HIAA.

Distinguishing impulsive from nonimpulsive violent criminality, Linnola found low CSF 5-HIAA in impulsive, but not premeditated, violent offenders (for example, homicide offenders) (4). The 17 offenders who had committed more than a single violent crime had mean 5-HIAA values lower than the offenders who had committed a single violent crime. Violent offenders who also had a history of suicide attempt had the lowest 5-HIAA levels. This study did not find any correlations between norepinephrine or other CSF monoamines and aggression.

Lower levels of CSF 5-HIAA have also been found in impulsive arsonists (29) and in violent criminal offenders (30). There have also been replications of this relationship between CSF 5-HIAA and impulsive aggression in animal studies (31).

Several studies have, however, been unable to find a correlation between 5-HIAA levels and aggression: 3 studies of subjects with personality disorder (32–34), 1 study of subjects

with attention-deficit hyperactivity disorder (ADHD) (35), and 1 study of a normal population (36). One possible reason for these discrepancies is the greater severity of aggression in the earlier study. In a metaanalysis of 5-HIAA studies of aggression, Balaban and others found that, when corrected for the confounding factors of height, sex, and age, 5-HIAA was correlated with the presence of a treated psychiatric disorder but not with particular behavioural indices (2). However, in its analysis the review grouped subjects in each study together and thus may not have been able to detect important differences.

Although CSF studies have the advantage of measuring neurotransmitters in the central nervous system, they are costly and involve discomfort on the part of the study subjects. There is also some question about how to interpret CSF levels of neurotransmitters as well as their probable lack of sensitivity to milder behavioural abnormalities. Other methodologies have tried to find physiological markers of 5-HT function. One such method is the neuropharmacological challenge, in which a challenge agent is administered and a response in the central nervous system (CNS) is measured.

The most widely studied challenge agent in this area has been fenfluramine. Administration leads to a release of synaptic 5-HT, resulting in a reliable limbic-hypothalamic-mediated release of peripheral prolactin (37). Fenfluramine is thought to activate limbic-hypothalamic postsynaptic 5-HT receptors, leading to the release of a prolactin-releasing factor that acts upon the pituitary lactotrophs to release prolactin. Studies have shown that the most likely mechanism of fenfluramine's release of 5-HT is via the 5-HT_{2A/2C} receptor subtypes, as evinced by blockade of prolactin response by 5-HT_{2A/2C} antagonists (38) and the parallel between fenfluramine's action and that of m-Chlorophenylpiperazine (m-CPP), which also acts on the 5-HT_{2A/2C} system (39). It is not blocked by the 5-HT_{1A} antagonist pindolol (40) or by the 5-HT₃ antagonist odansetron (41), involves newly synthesized 5-HT as evinced by tryptophan depletions studies (42), and is not via direct 5-HT stimulation of lactotrophs, because there are no known 5-HT receptors on the pituitary lactotroph cells (43). There is some evidence that fenfluramine's action may be specific to the 5-HT_{2C} receptor subtype, because in one study the 5-HT_{2A} antagonist amperozide did not have an effect on prolactin release after challenge (44).

Using fenfluramine challenge to test the hypothesized link between serotonergic function and impulsive aggression, Coccaro and others (45) gave a sample of patients diagnosed with either personality disorders or affective disorders a one-time 60 mg dose of d, l-fenfluramine and measured prolactin response after the dose was administered. Aggression was correlated with decreased prolactin response to fenfluramine in subjects with personality disorders. No correlation was seen in the patients with affective disorder, but

prolactin response to fenfluramine was reduced in all patients with a past history of suicide attempt.

This correlation of aggression with decreased responsiveness of the serotonergic system has been replicated in subjects with personality disorders (18,46,47), in antisocial violent offenders (48), in primates (49), in studies that use the more specific enantiomer d-fenfluramine (d-FEN) (40,50), and in patients with unipolar depression and anger attacks (51). Coccaro and others (39) found that while Life History of Aggression (LHA) scores in the patients with personality disorders were inversely correlated with prolactin response to d-FEN, no relation was found with basal levels of CSF 5-HIAA, raising the possibility that prolactin response to fenfluramine challenge may be a more sensitive marker of aggression than CSF 5-HIAA. Other probes of 5-HT function have had similar findings of diminished serotonergic function in various psychiatric populations. These have included 3 studies that found aggression to be inversely correlated with diminished prolactin response by the 5-HT_{1A} and 5-HT₂ agonist m-CPP (33,52,53). Self-reported aggression and history of aggression were correlated with diminished prolactin response to d-FEN and diminished cortisol response to ipsapirone challenge (54).

Although most studies using challenge methods to investigate serotonergic function have found an inverse correlation with aggression, several have found a direct relation. An early study by Meltzer examining, among other things, suicidality in patients with affective disorder, found that cortisol response to 5-hydroxytryptophan was greater in those patients who had made suicide attempts (55). Although this finding needs to be replicated, it is notable in that 5-hydroxytryptophan, like fenfluramine, is thought to act on the 5-HT₂-type receptor. Meltzer's findings were consistent with a denervation hypersensitivity of postsynaptic receptors, possibly in the context of global serotonergic hypofunction. This finding may be reconcilable with results from d-FEN challenges if it becomes evident that the 2 challenge agents are working on different receptor subtypes or different aspects of the serotonergic system.

Two studies have found a direct correlation of prolactin response to fenfluramine in substance abusers (56,57). In the 4 studies of children, 2 have found enhanced prolactin response to d-FEN correlated with aggression (58,59). Halpern was unable to replicate this (58), finding no observable relation, nor were Stoff and others in a study of prepubertal males (60). Although it is possible that the relation between serotonergic function and aggression changes through the life cycle, possibly due to an abnormal overexpression of 5-HT in early childhood (61), and may vary with comorbidities such as substance abuse, more work with different challenge agents needs to be done to verify these results.

An other in di rect method of study ing serotonergic func tion in the brain has been through ex am in ing the platelet, whose 5-HT_{2A} re ceptor is mo lec u larly ho mol o gous to the one in the brain (62). Plate lets are not part of the CNS, but the ra tio nale for study ing their se ro to nin re ceptors is that if they are mo lec u larly sim i lar to their CNS coun ter parts, they may share ab nor mal i ties in af fected in di vid u als, es pe cially to the de gree that these re ceptors are un der ge netic in flu ence. Most stud ies to date have found an in verse cor re la tion be tween the num ber of platelet bind ing sites and ag gres sion, al though there have been sig nif i cant non re pli cating stud ies and some stud ies with op po site find ings.

Stoff (1987) found lower num bers of 3H-imipramine–bind ing sites on plate lets of ag gres sive chil dren with CD when com pared with non ag gres sive chil dren with CD (63). Stoff was un able to re pli cate this find ing, al though it was re pli cated by Birmaher (64). Coccaro and oth ers (65) re ported an in verse cor re la tion be tween the num bers of platelet 3H-paroxetine–bind ing sites and life his tory of ac tual ag gres sive events.

In ad di tion to ge netic fac tors, the serotonergic sys tem is in fluenced by en vi ron men tal fac tors. The in fluence of en vi ron ment on ag gres sive be hav iour is com plex. Some of this in fluence may oc cur dur ing cru cial de vel op men tal phases, as seen in stud ies that show such early fac tors as birth com pli ca tions and ma ter nal re jec tion to be as so ci ated with early on set vi o lent be hav iour (66). Serotonin may be one of the medi a tors of en vi ron men tal in fluence on the brain. In an i mals, se ro to nin func tion has been shown to be in fluenced by chronic stress and glu cocorticoid lev els (67), an dro gen and es tro gen lev els (68), past so cial per tur ba tion (69), sta tus in the dom i nance hi er ar chy (70), and ma ter nal stress dur ing preg nancy (71). Al though to date hu man data are lim ited, changes in se ro to nin func tion have been as so ci ated with so cio eco nomic sta tus (72), sus tained child hood abuse in pa tients with bor der line per son al ity dis or der (BPD), and his tories of im pul sive ag gres sive be hav iour (73).

Norepinephrine

Evi dence in hu man stud ies for the role of norepinephrine (NE) in ag gres sion is lim ited. Brown and oth ers re ported a po si tive cor re la tion be tween the CSF con cen tra tion of NE's ma jor me tabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG) and life his tory of ag gres sion in 12 men with per son al ity dis or ders. In the same sta tis ti cal model, how ever, CSF 5-HIAA ac counted for most of the vari ance in ag gres sion (28). In con trast, Virkkunen and oth ers (29) re ported lower CSF MHPG in vi o lent of fend ers and in im pul sive ar son ists, com pared with healthy vol un teers—a re sult that was not re pli cated in sub se quent stud ies (74,75).

Dopamine

Evi dence for the role of do pa mine in crim i nal ity and ag gres sion is also lim ited. Re duced CSF con cen tra tions in vi o lent of fend ers com pared with normal con trols of the dopamine me tabolite homovanillic acid (HVA) were ini tially re ported

by Linnoila and oth ers in of fend ers with an ti so cial per son al ity dis or der (4). This find ing was not re pli cated by Virkkunen and oth ers (29,74), but re duced HVA con cen tra tions have been re ported as a func tion of re cid i vism in the of fender (75) and in the of fender's fa ther (30). Re duced HVA con cen tra tions have also been found in as so ci a tion with ag gres sion in ab stin ent al co hol ics and healthy vol un teers (76), al though there is some ques tion whether CSF HVA merely re flects CSF 5-HIAA drive (77).

Vasopressin

In an i mal stud ies, vasopressin has been im pli cated as a fa cil i ta tor of the ex pres sion of ag gres sion. In the golden ham ster, for ex ample, adminis tra tion of a vasopressin re ceptor an ta gonist re duces ag gres sive be hav iour (78). Fluoxetine, which causes re duc tion of ag gres sion in this model, re duces cen tral vasopressin lev els (79). Al though Virkkunen found no cor re la tion of CSF vasopressin con cen tra tion with life his tories of ag gres sion in a sam ple of 26 pa tients with per son al ity dis or ders, Coccaro found that CSF vasopressin cor re lates di rectly with life his tory mea sures of ag gres sion in sub jects with per son al ity dis or ders, even af ter ac count ing for the re la tion with PRL (d-FEN) re sponse (80).

Glucose Metabolism

Hypoglycemia has been as so ci ated with ag gres sion (81,82). Hypoglycemia is thought to lead to im paired cen tral neu ron al func tion and con se quent im pair ment in cog ni tive pro cesses and judge ment, which may in crease the risk of ag gres sion or im pulsiv ity (83).

Virkkunen has dem on strated that im pul sive vi o lent of fend ers with an ti so cial per son al ity dis or der (84) and of fend ers with in ter mit tent ex plo sive dis or der (75,85,86) have lower glu cose nadir af ter glu cose chal lenge, com pared with normal vol un teers. Her itability was sug gested by the find ing that im pul sive vi o lent of fend ers with crim i nal fa thers had lower glu cose nadirs than those with out crim i nal fa thers. How re ac tive hypoglycemia and 5-HT func tion are re lated in the ex pres sion of vi o lent ag gres sion is un clear.

Testosterone

The role of tes tos ter one in im pul sive ag gres sion is well doc u mented in an i mal stud ies, with some ev i dence that tes tos ter one may mod u late 5-HT_{1A} and 5-HT_{1B} ef fects on ag gres sion (87), but the role of tes tos ter one in hu man ag gres sion is less clear (88). Vi o lent ag gres sion in men, on the whole, seems more cor re lated with ab nor mal i ties of serotonergic func tion than it is in women (89). Some of this may be due to the mod u la tion of se ro to nin func tion by sex hor mones. In im pul sive vi o lent of fend ers, CSF free tes tos ter one has been re ported to be el e vated in an ti so cial, but not in ter mit tent ly ex plo sive, sub jects (75). More stud ies need to be done in this area.

Cortisol and Corticotrophin

The role of cortisol and corticotrophin in human aggression has had limited study to date. In 1985, Virkkunen reported that 24-hour urinary free cortisol was low in antisocial, but not in intermittently explosive or nonimpulsive, violent offenders (90). In another study, corticotrophin was reported to be significantly reduced in antisocial impulsive violent offenders compared with healthy volunteers, with a trend for intermittently explosive violent offenders to have reduced corticotrophin concentrations in comparison with normal controls (77).

Cholesterol

Low serum cholesterol has been implicated in violence and suicide since the late 1970s. Virkkunen reported low serum cholesterol concentrations among antisocial, compared with nonantisocial, subjects with personality disorders (91). In another study involving a large group of homicide offenders, Virkkunen demonstrated that impulsive violent offenders with antisocial personality disorder or intermittent explosive disorder also had lower serum cholesterol levels than did nonimpulsive violent offenders (92). Among the homicide offenders, lower serum cholesterol levels were inversely correlated with the presence of a personal history of suicide attempt, self-injurious behaviour, and the presence of paternal violence under the influence of alcohol.

A metaanalysis of randomized clinical trials of cholesterol-lowering interventions showed increased mortality due to suicide and violence (93), results that were replicated in some (94), but not all, studies (95).

Contradictory reports have also been published. For example, Apter and others (96) looked at 152 consecutive admissions to an adolescent psychiatric inpatient unit (96). Serum cholesterol in this study was positively correlated with adolescent patients who were currently suicidal. Continuing work is needed in this area that accounts for confounding factors such as patient age, sex, psychiatric comorbidities, health status, physical damage, medications, exercise, nutrition, and timing of cholesterol measurements.

Imaging Studies

Neuroimaging studies have found abnormalities of brain function that correlate with aggression. Raine and others (97) used positron emission spectroscopy (PET) to study brain activity during a continuous performance task in 41 murderers pleading not guilty by reason of insanity. He found that murderers had reduced metabolism in the prefrontal cortex, superior parietal gyrus, left angular gyrus, and in the corpus

callosum. Asymmetry was also noted in the amygdala, thalamus, and medial temporal lobe.

PET visualization of cerebral metabolism has been useful in validating theories linking brain function with behaviour. Using PET to examine the effects of fenfluramine challenge, Mann (98) found that in healthy volunteers, fenfluramine led to detectable increases in left prefrontal and left temporoparietal cortex metabolism, results repeated by Meyer (99), who showed that d-FEN led to bilateral frontal cortex activations and decreased activity of the temporal cortex and thalamus. Thus, the serotonin-releasing challenge agents fenfluramine and d-FEN have been shown to have specific actions on discrete areas of the brain. Looking specifically at impulsive aggression in subjects with personality disorder, Siever and others (100) examined 6 impulsive-aggressive patients and 5 healthy volunteers for response to d-FEN or placebo. In response to d, l-fenfluramine, volunteers showed increases in orbital frontal and adjacent medial frontal cortex, cingulate, and inferior parietal cortex. Conversely, patients with impulsive aggression, as determined by the "Module for Impulse Aggression Disorder," showed significantly blunted metabolic responses in orbital frontal, adjacent ventral medial, and cingulate cortex, but not in the inferior parietal lobe, when compared with their matched controls. Non-specific stress effects were ruled out by a patient-normal control comparison using placebo challenge. Similar results were found in a placebo-controlled study using d, l-fenfluramine challenge and PET neuroimaging in 5 patients with personality disorder and 8 healthy control subjects. Notably, the patients with personality disorders all had histories of suicide attempts or self-mutilation. Soloff and others (101) found greater response to serotonergic challenge in the orbital and medial prefrontal cortex of controls than in patients with BPD. Although both studies had relatively small sample sizes, they agree with the hypothesis that the highly serotonergically innervated prefrontal cortex may be involved in the regulation of impulsive aggression. In neither study was there a correlation between degree of depression and metabolic differences. There is further evidence of involvement of posterior regions of the cingulate cortex in aggressive borderline patients (102), consistent with the role of cingulate cortex in affective evaluation of incoming stimuli.

Studies of aggressive behaviour in subjects without psychiatric or criminal histories have found similar results. Studies of healthy men using PET and behavioural activation implicate the orbitofrontal cortex, the right anterior cingulate cortex, and the bilateral temporal lobes in the normal expression and experience of anger (103). Taken together, these results from neuroimaging studies are consistent with neuropathological reports of increased numbers of serotonergic receptors in the

frontal cortex of suicide victims. Most studies have found reduced maximum binding to the serotonin transporter (B_{max}) as well as increased binding to the postsynaptic 5-HT_{1A} and 5-HT_{2B} receptors in the prefrontal cortex of suicide victims (104–106). All positive findings have been replicated (107). There is also some evidence that neuron number and density in the brainstem dorsal raphe nucleus was higher in suicide victims than in control subjects, lending support to the notion that in these patients serotonergic dysfunction leads to increased numbers of serotonergic neurons (108). This dysfunction may extend to the second messenger system as well (109,110).

Psychopharmacology

A comprehensive review of psychopharmacological studies to date is beyond the scope of this paper. In summary, however, psychopharmacological studies to date have treated aggression as a dimension, or target symptom, in different diagnostic categories. Results are sometimes surprising and counterintuitive, because agents which might be effective in one context may prove ineffective or even deleterious in another. In some diagnostic categories, such as borderline personality disorder, dimensional aspects of behaviour may be clinically significant in conceptualizing psychopathology and guiding effective treatment. Especially in nonemergency settings, care should be taken to avoid unnecessary side effects by using the most specific agents possible to treat aggression while continuing to address other underlying psychopathology. To date, the most promising clinical strategies involve using mood stabilizers or selective serotonin reuptake inhibitors (SSRIs) in patients with personality disorders and stimulants in younger patients with ADHD or CD. Ongoing research into the medical treatment of impulsive aggression is needed, as are studies looking at the integration of behavioural and psychotherapeutic approaches.

Conclusion

Impulsive aggression has a role in both criminal and non-criminal behaviour. Although its forensic implications are still unclear, an impulsive crime is not synonymous with a nonpremeditated one. Data support the notion that it probably has a significant genetic, heritable component. A single gene for aggression has not been found. Further work may yet find a polymorphism, or combination of genes, that contribute to the expression of an impulsive-aggressive phenotype.

Impulsive aggression has many of the characteristics associated with temperament, including relative stability through life, expression early in life, and association with biological variables. The serotonergic system has been the most systematically studied of these variables. Findings of reduced levels of CSF 5-HIAA in association with violent criminality, deficits in serotonergic function as revealed by

Clinical Implications

- Central 5-HT function seems to be inversely related to measures of impulsive aggression in certain populations, such as adult personality-disordered patients.
- Impulsive aggression may be an aspect of personality that is relatively stable over a period of years, heritable, and correlated with biological variables.
- Outpatient treatment studies of impulsive aggression have favoured the use of antidepressants and mood stabilizers over sedative-hypnotics.

Limitations

- Central 5-HT is not the only neuro-modulator involved with impulsive aggression. Some others include norepinephrine, dopamine, vasopressin, and cholesterol.
- Impulsive aggression is a psychiatric concept. Its forensic implications are determined by legal definitions and not clinical ones.
- Some studies have failed to replicate the association of serotonergic hypofunction with impulsive aggression in specific groups of patients, such as substance-abusing patients and prepubertal patients with conduct disorder.

psychopharmacological challenge studies, and visualization of prefrontal cortex abnormalities in the brain and in brain function with neuroimaging technology have allowed a workable hypothesis to be made, linking serotonergic dysfunction with behavioural disinhibition and the expression of impulsive aggression. Although challenge studies in humans have emphasized the role of the 5-HT_{2A/2C} neuroreceptors, further investigation of the role of other serotonin receptor subtypes, other monoamines, hormones, and neuropeptides is needed.

Above the contribution of putative genetic factors, the serotonergic system is also very responsive to environmental factors, especially early disruptions in development and early exposure to abuse or trauma. In this sense, although biologically based, a theory of serotonergically mediated inhibition of impulsive aggression is not biologically deterministic because the influence of environmental variables as a modulator of serotonergic function is significant from moment to moment as well as over a lifetime, and serotonin's role in behaviour is only in the context of the complicated relationship between brain, mind, and environment.

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Resumé— La neuropsychopharmacologie de la criminalité et du comportement agressif

Bien que la notion selon laquelle le comportement agressif a des composantes biologiques ne soit pas nouvelle, la recherche récente en génétique, neuropsychopharmacologie et neuroimagerie a contribué à clarifier l'apport biologique au comportement agressif. Jusqu'ici, les études se sont concentrées sur la fonction sérotoninergique et le comportement agressif impulsif. Des études de provocation pharmacologique ont révélé une sensibilité sérotoninergique réduite associée au comportement agressif impulsif. Des études de neuroimagerie indiquent un rôle du cortex préfrontal de même que d'autres parties du cerveau dans l'expression du comportement agressif. La sérotonine n'est pas le seul aspect de la fonction cérébrale qui participe au comportement agressif impulsif, et d'autres travaux sont en cours sur d'autres neurotransmetteurs et neuropeptides.