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Abstract

Criminal behaviour and violence are increasingly viewed as worldwide public health problems. A growing body of knowledge shows that criminal behaviour has a neurobiological basis, and this has intensified judicial interest in the potential application of neuroscience to criminal law. It also gives rise to important questions. What are the implications of such application for predicting future criminal behaviour and protecting society? Can it be used to prevent violence? And what are the implications for the way offenders are punished?

Disciplines

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Neurocriminology: Implications for the Punishment, Prediction, and Prevention of Criminal Behavior

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Preface

Violence is increasingly viewed as a world public health problem. A growing body of knowledge shows that there is a neurobiological basis to violence, and this has intensified judicial interest in the potential application of neuroscience to criminal law. It also gives rise to important questions. What are the implications of such application for predicting future violence and protecting society? Can it be used to prevent violence? And what are the implications for the way offenders are punished?

Introduction

Advances in neuroscience are providing increased understanding of how our biology influences our behavior – for both good and bad. The emerging field of neurocriminology seeks to apply techniques and principles from neuroscience to better understand, predict, and ultimately prevent crime. Such an approach brings with it both the potential economic and social benefits of violence reduction and also neuroethical concerns[1].

In this Perspective, we discuss the current state of research in neurocriminology. We provide an overview of the neurobiological abnormalities associated with criminal behavior, and consider the genetic and environmental factors that may contribute to these abnormalities. We highlight studies conducted to date, many of which suggest that biological factors may aid in the prediction of future crime and violence. We then discuss implications for this research in the legal system.

The current state of neurocriminology

There are now relatively extensive literatures that document relationships between antisocial behavior and biological functioning. With exceptions[2], most studies are correlational and cross-sectional, and largely do not provide information on specific genetic or environmental factors that may mediate these relationships. However, an increasing number of prospective longitudinal studies are examining whether the presence of specific biological factors, whether they be hormone levels, neurotransmitter levels, physiological indices or brain deficits, is predictive of future offending. Because most studies define antisocial behavior and crime broadly without distinguishing between violent and non-violent offenders, this review largely concerns the broad propensity to criminal behavior.

Genetics

Results from well over 100 behavioral genetics studies with different designs — including twin studies, studies of twins reared apart, and adoption studies — have converged on the conclusion that there is a significant genetic basis to antisocial and aggressive behavior. Estimates of the variance that is attributable to genetics vary, but several meta-analyses place the level at between 40-60%[1]. Heritable influences, with some exceptions, are broadly consistent across gender and ethnicity[3]. Adoption studies in particular have the advantage of being able to truly separate genetic from environmental factors and provide a converging line of evidence that there are heritable influences on antisocial and aggressive behavior (BOX 1).

Recently, research has focused on identifying which *specific* genes confer risk for antisocial behavior. Several genetic variants have been identified that incrementally increase the risk for antisocial behavior[4-7]. Although approximately half of 185 studies have reported effects,

a meta-analysis revealed that no variant was associated with aggression at the 5% level of significance[8]. This finding underscores the idea that, as with other complex behaviors, the contribution of any single gene is likely to be quite small. It may be the combination of a larger number of gene variants that significantly increases risk for aggressive behavior. Knowledge about individual genes may prove useful in improving our understanding of the mechanisms and pathways that increase risk for antisocial behavior. Importantly, the environment plays an equally influential role. Indeed, some genetic variants confer risk for antisocial behavior only in the presence of particular environmental risk factors, such as abuse in early childhood[9]. Research in epigenetics[10] has shown that the environment can influence how genes are functionally expressed in an individual (and even in specific brain areas), a finding that undermines traditional arguments of biological determinism.

Prenatal and perinatal influences

Early health risk factors, sometimes in conjunction with social risk factors, have been found to be associated with increased probability that a young infant will develop antisocial and aggressive behavior. During the prenatal and perinatal period, a number of factors may be important. Birth complications, in combination with maternal rejection of the child in the first year of life, have been associated with violent criminal offending at age 34 in a Danish sample[11]. These predictive findings have been replicated in the U.S., Canada, Sweden and Finland with respect to adult violence, and in Hawaii and Pittsburgh with respect to childhood antisocial behavior[1]. Five other studies have shown associations between birth complications and externalizing behavior problems in children[1]. Fetal maldevelopment during the second trimester of pregnancy, as indicated by resulting minor physical anomalies in the child (features such as low seated ears or a single palmar crease) has been associated with later violent delinquency[12] and adult violent offending[13]. The association between fetal neural maldevelopment and childhood aggression and adolescent conduct disorder may be even more pronounced when combined with effects of poor parenting[14] or social adversity[15] . Criminal offending and psychopathy have been associated with another indicator of disruption in fetal development, namely cavum septum pellucidum (CSP)[16], which is the failed closure of the septum pellucidum, a process that normally takes place during gestation until approximately six months post-birth.

CSP is thought to be an early marker for disrupted development in the limbic region of the brain[17], which in turn is associated with offending[18].

Maternal nicotine consumption and alcohol consumption during pregnancy are also factors that may predispose to violent offending in adulthood — findings that have been replicated across many studies in several continents[1, 19]. Even small amounts of alcohol during pregnancy (one drink / week) have been associated with increased childhood aggression in the offspring[20]. There is current debate as to whether nicotine exposure predisposes to offending by causing hypoxia in the fetus that results in brain impairment, or whether this association is genetically mediated[21, 22].

Lead levels have been associated with juvenile delinquency and aggressive behavior, findings which have been documented in at least six studies[23]. From a prospective viewpoint, high lead levels in the mother during the first and second trimester of pregnancy are associated with increased risk for arrest for violent crimes in adulthood[24]. High dentine lead levels assessed at ages 6-9 years have been associated with increased violent offending at ages 14-21 years, with poorer cognitive functioning mediating this relationship[25]. Some studies have carefully controlled for potential confounds such as poverty, maternal smoking, alcohol use, and drug use, and have shown that these findings apply to women as well as men[24, 25]. Higher manganese levels in the mother during pregnancy have also been associated with increased externalizing behavior problems (aggressive, destructive, defiant) at age 8-9 years[26].

Poor nutrition in either the first or second trimester of pregnancy has been associated with a 2.5-fold increase in antisocial personality disorder in the offspring[27]. Malnutrition in infancy is associated with conduct problems in adolescence, a relationship that is partly mediated by low IQ[28]. Similarly, children with signs of malnutrition at age 3 have higher rates of aggressive and antisocial behavior at ages 8, 11, and 17 years [29] over and above any contribution from social risk factors. This relationship was also mediated by low IQ. These findings suggest that a number of early environmental factors, likely via effects on biological systems, may increase the risk for antisocial behavior as late as adulthood.

Hormones and neurotransmitters

The steroid hormones cortisol and testosterone have been the most intensively researched hormones in relation to antisocial behavior. Disruptions in the hypothalamus–pituitary–adrenal

(HPA) axis, the body's stress response system that releases the hormone cortisol, are frequently observed in antisocial persons. Associations between antisocial behavior and cortisol levels vary depending on the type of antisocial behavior and other factors[30]. Psychological stress at various stages in development may produce lasting changes in HPA axis functioning and thereby predispose an individual to antisocial behavior[31]. Low levels of cortisol in childhood are predictive of aggressive behavior five years later, in adolescence[32]. Similarly, a study showed that boys identified as having behavioral problems who had low cortisol levels were more aggressive at a two-year follow-up [33].

Increased testosterone levels have been repeatedly associated with increased aggressive behavior in adults. Caveats include the fact that this relationship appears to be less evident in pre-pubertal samples[31], and meta-analyses of this relationship find a small effect size of r =.08[34]. Some randomized, placebo-controlled cross-over trials have shown that testosterone administration increases aggressive behavior in adult males[35] suggestive of a causal connection, although other experimental studies using lower doses of testosterone have not shown an increase in aggressive behavior[36]. Increased levels of testosterone at ages 10-12 are predictive of assaultive behavior at ages 12-14, norm-violating behavior at age 16, and cannabis use at age 19[37]. Higher levels of testosterone at age 16 are associated with crime in adulthood[38].

Multiple neurotransmitter systems have been implicated in aggression[39], and the best-replicated correlate of human aggressive behavior is low serotonin level[40]. Low levels of cerebrospinal fluid (CSF) serotonin particularly characterize persons showing impulsive aggressive behavior[41]. Experimental manipulations that reduce serotonin levels in the brain (acute tryptophan deletion) reduce functioning of the orbitofrontal cortex during an inhibitory motor control task[42], a region commonly implicated in antisocial behavior[43]. However, aggression has also been associated with reduced monoamine oxidase A (MAOA) levels in the brain. MAOA is an enzyme that breaks down serotonin and other neurotransmitters and a reduction would presumably result in higher serotonin levels[44]. This seemingly contradictory finding demonstrates the need for studies to simultaneously examine multiple biological markers in order to obtain information about how neurotransmitters may interact with one another to increase risk for aggression.

Psychophysiology

Psychophysiological differences have also been observed between antisocial groups and control groups. Meta-analyses and reviews conclude that low resting heart rate is probably the best-replicated biological correlate of antisocial and aggressive behavior in children and adolescents[45, 46]. Low resting heart rate may indicate a lack of fear and a reduced likelihood of experiencing negative affect in response to a criminal act [45, 46]. Low heart rate in childhood and adolescence has been associated with adult crime in all four longitudinal studies conducted to date[45]. Across these studies, low resting heart rate was found to be as strong a predictor of future antisocial behavior as it is of current antisocial behavior[45]. In delinquents who were arrested for a minor offense at age 14, attenuated heart rate responses to a stressor were associated with both a shorter time to re-offend, as well as with a greater number of re-offenses within a five year period[47]. Another study showed that low heart rate at age 18 is predictive of conviction frequency and violence up to age 50, after multiple confounds had been controlled for[48].

Psychophysiological indicators of under-arousal — such as slow-frequency electroencephalographic activity and reduced skin conductance activity — at age 15 are predictive of crime at age 24[49]. A recent meta-analysis[50] has documented reduced amplitude of the P300 event-related brain potentials, which is thought to reflect inefficient recruitment of neural resources during information processing, in adult antisocial populations. Similarly, reduced P300 amplitudes at age 11 have been associated with criminal offending at age 23. P300 amplitudes predicted offending at age 23 over and above measures of child antisocial behavior at age 11[51].

Poor autonomic fear conditioning — the ability to learn associations between neutral cues and aversive stimuli — is another well-replicated correlate of adult criminal and psychopathic adult offending[52, 53], conduct disorder in children and adolescents[54, 55], and juvenile offending[56]. A review of 46 human brain imaging studies suggests that deficits in fear conditioning may reflect abnormalities in a common core fear network consisting of the amygdala, insula, and anterior cingulate[57]. Indeed, numerous brain imaging studies find abnormalities in these areas in antisocial persons, although this has been disputed with respect to individuals with psychopathic traits[58], a specific subgroup of criminal offenders. Poor electrodermal fear conditioning at age 3 is associated with convictions for criminal offenses at age 23[59]. In addition to aiding in the prediction of future offending, individual differences in fear conditioning may also provide information about which antisocial individuals may desist from future violence, or be

particularly amenable to treatment. For example, adolescents who were identified as being at risk for adult crime by virtue of being antisocial at age 15, but who did not go on to develop into adult criminal offenders at age 29 showed superior fear conditioning compared both to antisocial adolescents who become offenders and to non-criminal controls[60].

Brain imaging and neurology

Reduced functioning in the frontal lobe of the brain is to date the best-replicated brain imaging correlate of antisocial and violent behavior. In particular, a recent meta-analysis of 43 structural and functional imaging studies found that the largest reductions in structure and function within the frontal lobe of antisocial individuals were observed in the orbitofrontal cortex, anterior cingulate cortex, and dorsolateral prefrontal cortex[61]. The dorsolateral prefrontal cortex is associated with self-regulatory processes including attention and cognitive flexibility, and may be linked to the antisocial features of impulsivity and poor behavioral control[61]. The anterior cingulate is involved in error processing, conflict monitoring and avoidance learning[62-64]. Individuals with damage to this region are more disinhibited and aggressive[65] and demonstrate impairments in inhibitory control and emotional processing [66, 67]. The ventral prefrontal cortex, including the orbitofrontal cortex, has received particular attention given its role in emotional processing, learning from reward and punishment, and decision-making[68, 69].

The possibility of a causal connection between impaired orbitofrontal cortex structure and/or function on the one hand, and crime and/or violence on the other, has been raised by neurological studies which show that head injury in ostensibly normal individuals precedes the onset of disinhibited antisocial behavior. For example, higher levels of aggression were found in war veterans who had experienced penetrating head injuries localized to the ventral prefrontal cortex[70]. Furthermore, neurological patients who had suffered accidental head injury to the ventral prefrontal cortex show poor decision-making, reduced autonomic reactivity to socially-meaningful stimuli, and psychopathic-like behavior[68]. In a particularly striking example, a tumor in the orbitofrontal region preceded the onset of pedophilia in an individual; after resection of the tumor, the person's behavior returned to normal (BOX 2)[71].

The amygdala is another brain region that is consistently identified as showing altered activity in brain imaging studies of antisocial individuals. The type of deficit may vary in different subgroups of antisocial individuals. Adults and youth with psychopathic traits, who

have blunted emotional responding and may engage in more cold, calculated aggression, have reduced amygdala volume[72] and functioning[73-75], whereas individuals with a more impulsive, reactive form of aggression demonstrate exaggerated amygdala reactivity[76]. Reduced amygdala volume in psychopathic individuals has been localized to the basolateral, lateral, cortical, and central nuclei — regions involved in emotional processing, fear conditioning and autonomic reactivity to affective stimuli[72]. Of note, patients with damage to the amygdala have a reduced sense of danger, are less fearful[77], and have deficits in recognizing fearful facial expressions[78] (a process involved in experiencing empathy). The association noted earlier[59] between poor classical conditioning in childhood and crime in adulthood suggests, but does not prove, a causal relationship between amygdala functioning and antisocial behavior.

Most brain imaging studies are essentially correlational and cross-sectional, and until recently no longitudinal brain imaging research on antisocial populations has been conducted. Two recent studies have indicated the potential for neuroimaging to provide incremental predictive power in predicting re-offending. One study showed that reduced functioning in the anterior cingulate during a go/no-go task in prisoners doubled the likelihood of re-arrest three years later[79]. A second study of high-risk community males showed that reduced amygdala volume at age 26 was associated with violent offending three years later[18]. As has been observed in other biological longitudinal research, both studies showed predictive utility of brain measures over and above past history of antisocial behavior and other confounds.

Other longitudinal studies have shown that incurring brain damage increases the risk for criminal behavior. A longitudinal study of 231,129 individuals from Sweden documented a three-fold increase in violent crime following traumatic brain injury after adjusting for demographic confounds[80]. A prospective longitudinal study of 12,058 individuals from Finland showed that traumatic brain injury (TBI) during childhood and adolescence was associated with a 1.6 fold increase in crime in adulthood after controlling for confounds; children suffering TBI before age 12 starting their criminal careers significantly earlier compared to those who suffered TBI after age 12[81]. These studies demonstrate that information about brain structure and function, regardless of whether the origins are neurodevelopmental or a result of direct physical insult later in life, may be of some use in identifying which individuals are at increased risk for criminal behavior.

Remaining challenges for research on biological risk factors for violence and crime

In sum, in recent years, evidence of the importance of biological factors in antisocial behavior has accumulated and is being recognized as valuable in our understanding of crime and violence. With advances in neuroscience and the design of longitudinal investigations, studies are becoming methodologically stronger. Taken together, it is becoming increasingly harder to argue that biological factors do not predispose some individuals to adult crime. This conclusion neither diminishes nor replaces social and environmental perspectives on crime causation[24, 29, 80]. Together, genetic and environmental factors shape the way that biological systems develop and function and thus affect multiple complex psychological processes that are important in controlling and regulating behavior and in behaving morally.

Important gaps in our knowledge remain. Very little is known on the neurobiology of regulatory crimes, and one study has observed structural and functional prefrontal enhancements, as opposed to impairments, in white collar criminals[82]. A future challenge in neurocriminology lies in parsing out which specific genetic and environmental influences result in what neurophysiological changes that result in the more proximal cognitive, affective, and behavioral risk factors for violence. What neurobiological processes mediate the relationship between the well-documented early social risk factors and violence in adulthood? A few studies have begun to explore how genetic and environmental factors affect the brain. For example, researchers have found that the adolescent offspring of mothers who smoke during pregnancy demonstrate reduced thickness in two regions of the brain that have been implicated in antisocial behavior – the orbitofrontal cortex and middle frontal cortex[83]. Children exposed to high levels of lead early in life have been shown in adulthood to have reduced grey matter volume in the brain, particularly in the prefrontal cortex[84]. Males with a common polymorphism in the monoamine oxidase A (MAOA) gene (present in about 30% of the population) have an 8% reduction in the volume of the amygdala, anterior cingulate and orbitofrontal cortex [85], suggesting a causal pathway from genes to brain to antisocial behavior. To better delineate these types of causal connections, future studies need to examine the pathways by which genes and environment affect biological systems, and how these altered systems in turn predispose to antisocial behavior.

A predisposition to criminal behavior is unlikely to be reduced to one or even two simple brain circuits, but likely involves multiple brain dysfunctions and multiple circuits that each give rise to different risk factors for violence. Thus, the future use of brain imaging in the assessment

of risk for criminal behavior will require a much more sophisticated understanding of these circuits. Although brain imaging techniques have advanced rapidly in the last few decades, there are still many limitations to these methods[86]. However, with continued methodological improvements in neuroscience research, we will gain more information about how brain regions function together to predispose to criminal behavior.

Although only a few prospective longitudinal studies have been conducted, findings from research on early risk factors suggest that information about biological factors in youth may aid in the prediction of which individuals are more likely to engage in crime and violence later in life. Such information may also help identify individuals who are particularly amenable to rehabilitation. In a review of ten studies implementing variants of cognitive-behavioral therapy in individuals with antisocial behavior[87], multiple neurobiological factors were predictive of treatment response and progress, including heart rate, hormone levels, and neuropsychological measures of risk-taking, sensitivity to negative consequences, impulsivity, cognitive flexibility, and emotion processing. Although such initial findings are provisional, these neurobiological characteristics could ultimately help to determine which offenders are best suited to specific rehabilitation programs and more safely re-integrate into society. A major challenge that remains to be addressed is to identify socially acceptable psychosocial or biological intervention programs that target biological risk factors for criminal behavior.

The Legal Context

Neurocriminology interfaces with the judicial system at three main levels: punishment, prediction and prevention. To what extend does the growing body of knowledge on the neuroscience of crime and violence suggest that we should rethink our approach in these three domains? Although it is unlikely that neurocriminology will result in any radical or swift shift in the operation of the criminal justice system in the very near future, it is not inconceivable that some modest change may occur in these areas at some point, assuming the field continues to develop and evolve, as the past two decades have suggested.

Punishment

Punishment is predicated on blameworthiness. The extent to which we blame individuals is a function of the extent to which they can be held accountable for their actions. Such accountability in a legal context is predicated on the concept of responsibility.

In this context, let us assume that to some extent neurobiological abnormalities or insults relatively early in life predispose some individuals to a life of crime and violence. We will also assume that offenders are not responsible for being exposed to these early risk factors for violence. Are they responsible for their behavior, and if so, to what degree? In the case of Michael, in whom a tumor in the orbitofrontal region preceded the onset of pedophilia, which disappeared after the tumor had been removed (BOX 2)[71], was he responsible for his pedophilia?

Currently in the United States, an individual is deemed 'responsible' for their actions if two conditions are met: first, they have sufficient rational capacity; and second, they are not acting under coercion. Rational capacity is typically interpreted as whether the individual knew what he or she was doing, and understood that his or her actions would have consequences. Michael's (Box 2) is a telling case because the temporal ordering of events — from normality to brain tumor to pedophilic interest to tumor resection to normality, and back again — is suggestive of causality in a single case. However, in his own words, Michael admitted, "…somewhere deep, deep, deep in the back of my head, there was a little voice saying 'You shouldn't do this'"[88]. He knew at the time of the act what he was doing, and he also knew that what he was doing was wrong. In the eyes of the law, Michael was legally responsible for his actions.

Given that Michael would be considered legally responsible, it is even harder to argue that an individual with a less obvious neurobiological 'predisposition' to offending than Michael's — whether that be reduced functioning of the amygdala during a moral decision-making task, carrying a specific variant of the MAOA gene, or a significant but less visibly obvious volume reduction in prefrontal gray matter — is not responsible for his or her actions. In most criminal cases, the causal flow from biological risk to offending will never be known. All behavior is caused, and identifying the brain basis to behavior does not in itself establish that the individual had diminished rational capacity[89]. Therefore, as the law currently stands in the United States and other countries, the documentation of neurobiological risk factors, no matter how early in life they originate, does not render that individual lacking responsibility.

Despite this current legal stance, a challenging question concerns whether the current law pertaining to responsibility is in need of modest revision. This is ultimately a normative question over which there can be reasonable disagreement. Quite independent of any appeal to neurobiological risk factors, it has been argued that severe psychopaths should not be held responsible on the grounds that they have no sense of moral rationality — they are not sensitive to moral concerns and thus do not have the moral sense of most people in society[90]. Add to that persuasion an increasing body of evidence showing that neurobiological factors contribute to criminal psychopathy in adults as well as to behavior in children with psychopathic-like traits[91], the suggested revision perhaps becomes more compelling, particularly in a case where an individual has several documented neurobiological and psychosocial risk factors for violence potential, as in the case of Donta Page (BOX 3).

The judicial system acting in a practical world essentially conducts binary decision-making, for example, in establishing innocence versus guilt. Determination of diminished capacity in the U.S. similarly involves a categorical judgment on the presence or absence of a mental disability. This can be reasonably questioned. The widespread consensus of experts is that crime and antisocial behavior are dimensional constructs, not categorical[92] . Risk factors associated with antisocial and criminal violence are also usually dimensional in nature (e.g., degree of prefrontal dysfunction, level of resting heart rate), although some may be categorical (presence of traumatic brain injury, genetic polymorphisms). Unlike the U.S., the judicial practice in the Netherlands is guided by a five-point scale for assessing *degree* of criminal responsibility, with evaluations including personality and neuropsychological testing[93]. Thus, although neuroscience has no current definitional bearing on concepts of responsibility, it is not without international precedent to consider a revision to legal practice in the U.S., U.K., and other countries whereby responsibility may in the future be assessed on a continuum using measures that include neurobiological variables.

Although a sensible dividing line needs to be drawn for practical reasons, in theory one can conceive of a set of multiple neurobiological and genetic influences, combined with social influences, which diminish responsibility to varying degrees. To the extent that neuroscience provides reliable methods to objectively document these influences, and assuming that methodologies become less expensive and quicker and easier to implement than hitherto, we anticipate that responsibility will eventually be conceptualized more broadly than it is today. For

example, although cognitive intelligence is the benchmark used by the law to document the capacity for rationality, the relatively new fields of affective psychology and neuroscience are providing us with evidence that emotion informs decision-making[68, 94] — a finding that is not yet instantiated in the law. Can individuals therefore be fully responsible when the feeling for what is moral is diminished? What may be just as important as *knowing* the difference between right and wrong when making moral decisions is having the *feeling* of what is right and wrong. As recent studies have documented in psychopaths, some individuals may have deficits in brain regions that are important for generating these emotional responses (BOX 4).

The facts that research in the field uniformly recognizes significant affective impairments as a core feature of psychopathy and that there is no longer any reasonable doubt that such affective impairment influences behavior[95, 96] raise the question of whether the legal system will eventually reformulate its current, longstanding concept of responsibility. For example, environmental head injuries can change an otherwise responsible individual into a person who, although capable of differentiating right from wrong, lacks the neural regulatory affective and behavioral control over their behavior[97]. It has been suggested that as neuroscience begins to offer a more detailed and specific account of the physical processes that can lead to irresponsible or criminal behavior, the public perception of responsibility may begin to change in the same way that public viewpoints on addiction have shifted from addiction as a failure of personal responsibility towards addiction as a disease[98].

Prediction

If biological factors could predict future violence over and above predictions based on social variables, even opponents of a neuroscientific perspective on crime would have to agree that neurobiology has added value. Whether or not such biological factors are causes or merely correlates of violence is irrelevant to the issue of prediction — the fact that they add predictive value is the currency of risk assessment in prisoners who are about to be released.

Given that approximately 50% of the variance in aggressive and antisocial behavior can be explained by genetic influences would appear to make a compelling case for using biological information to improve violence prediction. However, as genome-wide studies have largely failed to identify specific genes that can account for more than 1% of the variance in any complex behavioral trait gives considerable pause for thought[99, 100]. Molecular genetic advances

have, in theory, the potential to better elucidate and identify specific genetic factors predisposing to crime in the future, but currently the value of genotyping individuals to predict future violence is limited.

Perhaps surprisingly, endophenotypes such as prefrontal dysfunction and low heart rate, which reflect compound genetic and environmental influences, may currently explain more of the variance in adult violence than any individual genotype, and may have more traction in predicting future violence. The literature reviewed above has revealed several replicable early biological correlates of later violence. Some studies have shown that neurobiological markers can predict, over and above well-replicated psychosocial risk factors, which individuals will demonstrate antisocial or psychopathic traits[101, 102]. The two recent imaging studies described above[18, 79], together with multiple studies identifying psychophysiological and hormone predictors of future offending, provide some support for the conclusions made in a Royal Society report that neuroscience may have future value in predicting reoffending[103].

Despite the potential promise, and indeed likelihood, that neurobiology could provide at least modest increases in predictive power, methods used to predict the potential of future reoffending in about-to-be released prisoners have so far never incorporated neurobiological markers into the risk assessment equation. There are three main reasons for this. First, the evolving body of knowledge on neurocriminology has not yet become accepted in the social sciences and amongst practitioners. Second, neurobiological measures are less easy to collect than behavioral, social and psychological data. Third, there have been longstanding ethical concerns about collecting biological data on offenders. This may change given that DNA is now collected on all arrestees in the U.S. Technical developments are also increasingly making neurobiological risk assessments more feasible and practical and some, such as resting heart rate, are already incorporated into standard medical practice at the community level.

Any significant advances in predicting future violence will be based not just on progress in neurocriminology, but also on statistical advances. Machine-leaning techniques such as random forest have already been documented to improve the prediction of future charges of homicide or attempted homicide using traditionally available demographic and social variables[104]. If neurocriminology can identify replicable biological risk factors that provide incremental knowledge over and above the traditional variables that are currently used in dangerousness assessments, this would further aid violence prediction. Indeed, given that

probation and parole decisions must be made every day in offender populations, and assuming that neurobiological data can reliably enhance the accuracy of such predictions, it could be viewed as ethically questionable *not* to use such knowledge. However, such a development would raise several powerful ethical concerns. The potential for future extension of such prediction from offender populations to non-offender community populations is one such concern given the egregious civil liberty violations that could arise from false positives – that is, non-dangerous individuals being predicted to be at risk of committing crimes.

Intervention and prevention

If neurocriminology could provide even very modest insights into how future offending can be reduced, it would gain significant traction in the contexts of law and society in general, given that rehabilitation is a consideration in sentencing criminal offenders. Research in this area is currently sparse, but some studies are suggesting that neurobiological research can inform practice and give guidelines for future research.

At the psychopharmacological level it is known from over 45 randomized controlled trials that that a wide range of medications — including atypical antipsychotics, mood stabilizers, stimulants, and anti-depressants — are effective in reducing aggressive behavior in children and adolescents[105]. Although such effects may in part be due to the treatment of clinical conditions comorbid with aggressive behavior, such as ADHD and depression, pharmacological intervention is also effective in children presenting solely with aggressive symptoms. In adults with impulsive aggression, treatment with SSRIs has been found to increase glucose metabolism in the orbitofrontal cortex[106], suggesting a potential method for improving functioning in regions that have been identified as deficient in antisocial populations.

Despite these findings, there appear to be few, if any, systematic studies on the long-term efficacy of medications or their application to offender populations. Controversially, anti-androgen medications such as medroxyprogesterone or Depo-Provera are thought to reduce recidivism in sex offenders[107], but well-controlled randomized controlled trials are lacking. There is agreement that anti-androgens do reduce sexual drive, and in practice at least eight states in the U.S. have laws on chemical castration. Although some have argued that chemical castration violates the constitutional rights of the offender, others have countered that these medications are effective, that offenders are capable of making an informed decision, and that

preventing such informed choices with appropriate safeguards in place is ethically questionable[108].

A more socially acceptable avenue of biological intervention may lie in nutritional supplementations such as omega-3 fatty acids. Several studies have documented initial effectiveness in reducing antisocial and aggressive behavior in child and adult populations[109-111], although null findings exist[112]. The only two randomized controlled trials conducted in prison populations have documented a 34-36% reduction in serious offending in young offenders[109, 110]. Long-chain fatty acids are critical for brain structure and function, making up 30% of the cell membrane and being known to enhance neurite outgrowth and prolong cell life[113]. Given the existence of structural and functional neural correlates of antisocial and violent behavior and the finding that poor nutrition is an early risk factor for antisocial and aggressive behavior, omega-3 supplementation may prove to be modestly beneficial for at least some subgroups of offenders.

From a public health perspective, applications of neurobiological research on violence at the population level relatively early in life may help prevent adult violence. One randomized controlled trial for low-income pregnant mothers provided prenatal and early postnatal home visitations from nurses who provided advice on reducing smoking and alcohol use and improving nutrition. The study documented a 63% reduction in the number of convictions among the 15-year-old children of these mothers[114]. One experimental environmental enrichment that provided better nutrition, more physical exercise, and cognitive stimulation to community children aged 3-5 years documented increased electrocortical arousal and autonomic orienting at age 11 years, and a 34.6% reduction in offending rates at age 23[115]. In principle, targeted investment of resources to underserved populations at risk for future violence has the potential to enhance neurocognitive functioning and prevent offending, although these initial public health prevention programs require replication and extension.

Novel, innovative approaches to crime prevention through benign brain manipulation also have the potential to develop from basic neuroscience research. One recent experimental transcranial magnetic stimulation study shows that enhancing neural excitability of the right lateral prefrontal cortex increases compliance to social norms enforced by punishment[116]. Because crime is a failure to comply with punishment-enforced social norms, and because brain imaging research has documented reduced lateral prefrontal functioning in antisocial groups[61], enhancing prefrontal function could, as argued by others, have implications for crime prevention,

albeit at a potential cost of reduced compliance to norms not sanctioned by punishment[116]. Mindfulness training has also been shown to experimentally enhance both prefrontal and amygdala functioning[117, 118], and has been claimed to reduce aggression in offenders[119, 120]. We caution that this potential for crime prevention is extremely preliminary, but logically follows from our review of biological risk factors, legal implications, and prevention measures. Many would agree that once we can successfully treat offenders, significant changes in the law and our social perspective on crime will inevitably ensue.

Conclusions and future directions

Neurocriminological research in particular, and neuroscience in general, are *not* yet poised to make immediate changes in the prediction, prevention and punishment of criminal offenders. It is also unclear how strong and well-replicated scientific findings should be for their proper use in legal cases, although most evidence can be entered as mitigating factors in the penalty phase of a capital case. At the same time, notwithstanding difficulties in documenting causality, there is increasing convergence from different disciplinary perspectives that neurobiological influences partly predispose an individual to offending. Our considered opinion is that it would be valuable for researchers and practitioners to focus efforts on (1) the development of innovative and benign biological programs for crime prevention, (2) attempting to enhance the prediction of recidivism, with socially acceptable accuracy, by including neurobiological predictors, (3) including emotion alongside cognition in how we legally conceptualize responsibility, (4) considering the adoption of a dimensional concept of partial responsibility, and (5) discussing the thorny neuroethical implications of this growing body of neurocriminology research that includes the potential for medicalization of crime (e.g., viewing crime as the result of psychological deficits), stigma, and labeling (i.e., the potentially harmful effects of identifying individuals based on early biological predispositions)[98]. In the final analysis, there is initial proof of concept that neuroscience can become a significant future influence in society's approach to the punishment, prediction, and prevention of criminal behavior.

Box 1. Genetics and the intergenerational transmission of violence

Jeffrey Landrigan had been adopted at birth into a loving middle-class professional family. He was nevertheless a particularly troublesome child from the beginning. This behavior progressed from temper tantrums at age 2, abusing alcohol at 10, being arrested for burglary at age 11, abusing drugs as a teenager, to killing his first victim at age 20. After escaping from prison he perpetrated his second killing and was sentenced to death. While he was on death row in Arizona for this second homicide, another death-row inmate noticed an eerie resemblance between Jeffrey and Darrel Hill, an inmate he had met on death row in Arkansas. It transpired that Darrel Hill was the biological father of Jeffrey Landrigan — a father Jeffrey had never met.

Darrel Hill, like his son Jeffrey, was a career criminal who also abused drugs and also killed twice. Hill's father — Jeffrey' grandfather — was also an institutionalized criminal who had been shot to death by police. Jeffrey's great-grandfather was a notorious bootlegger. Darrel Hill saw Landrigan only briefly as Hill hid two .38 pistols and the narcotic medicine Demerol under his baby son's mattress — an action that was unintentionally prophetic of Landrigan's future drug abuse and violence.

As a fourth-generational criminal, Landrigan's case documents not just the intergenerational transmission of violence, but also illustrates how the adoption design separates the genetic influences of the biological parents from the environmental influences of the rearing home. Recent findings based on 43,243 adoptees and 1,258,826 non-adoptees unequivocally confirm that having a biological parent convicted of a violent crime raises the likelihood of criminal violence in the adoptee[121]. Taken together with findings from behavioral genetics studies documenting heritability for aggression in children, adolescents and adults, these findings indicate that there is a genetic contribution to criminality.

Box 2. Ventral prefrontal dysfunction, pedophilia, and legal responsibility

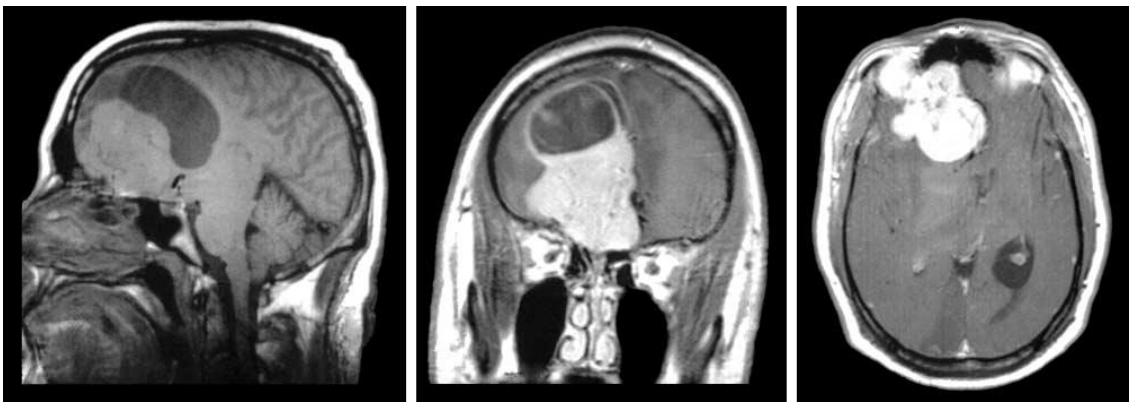
Cross-sectional brain imaging studies are correlational and cannot prove a *causal* association. Individual case studies can, however, be suggestive of causality.

Michael was a 40-year old schoolteacher and past correctional officer. He was happily married to his wife and loved both her and Christine, his stepdaughter. He had no prior history of criminal or deviant behavior. Michael began to change. He became uncharacteristically aggressive with his wife and began taking pornography to school. His bedtime rituals with his pre-pubescent step-daughter, which had previously consisted of singing lullabies, became more sordid and eventually he got into bed with her. He was found out and convicted of child molestation.

Michael had to decide between a prison sentence and a treatment program. He chose the treatment program, but was expelled after propositioning female staff. The night before he was due to be transported to prison, he went to the emergency room complaining of a severe headache. There he continued to solicit sexual favors from staff.

An astute neurologist ordered an MRI scan after Michael wet his trousers without showing any apparent concern. The MRI revealed a tumor growing from the base of the orbitofrontal cortex (see the figure). After the tumor was resected, Michael's behavior returned to normal and he was reunited with his wife and stepdaughter. After several months of normal behavior, his wife discovered child pornography on his computer. Michael was re-examined and it was discovered that the tumor had regrown. It was resected for a second time, and for at least six years after the resection Michael's behavior has returned to normal.

The case comes almost as close as one can get to a causal connection between ventral prefrontal brain pathology and deviant behavior – a pendulum moving from normality to brain dysfunction to pedophilia to neurosurgery to normality, and back again. In the face of the order in which events occurred, was Michael responsible for his inappropriate sexual behavior with his step-daughter?

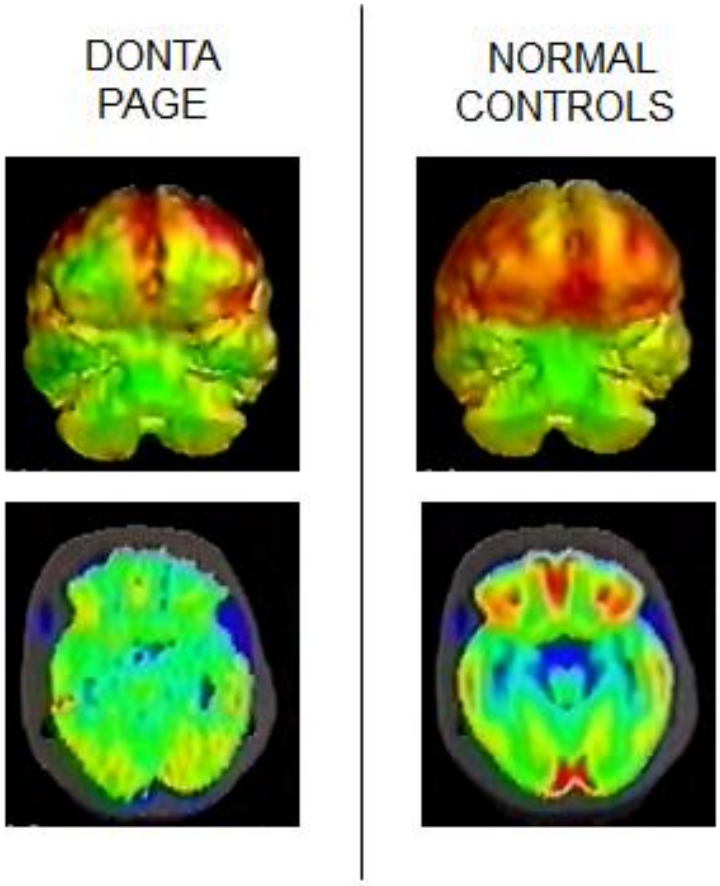


Box 2 figure. Magnetic resonance imaging scans of Michael's brain at the time of initial neurologic evaluation depicting a tumor mass displacing the right orbitofrontal cortex. Reprinted from Burns & Swerdlow[71].

Box 3. Neuroscience in the Courtroom

Donta Page, a young African-American male, brutally raped and murdered Peyton Tuthill, a young white woman living in Denver in 1999. The defendant was brought across state lines to be scanned in the same PET scanner with the same challenge task used in one prior study that had shown prefrontal dysfunction in murderers[11]. A comparison of the defendant's brain scan with the average of 56 normal controls showed reduced activation in the ventrolateral, ventromedial, and polar prefrontal cortex (see the figure). The author (AR) testified in the ensuing court case that such brain dysfunction, potentially arising from documented severe physical abuse and head injuries in childhood, could predispose to poor decision-making, lack of self-insight, lack of affect and poor behavioral controls, which in turn predisposes to callous, disinhibited behavior. Inter-racial homicide is relatively rare and may have polarized the jury, who found the defendant guilty of first degree murder with deliberation, punishable by death. In the death penalty hearing a three-judge panel accepted the reasoning that impaired capacity due to brain dysfunction — in conjunction with multiple additional biosocial predispositions to violence that also included parental neglect, extreme poverty, sexual abuse, poor nutrition, low heart rate and lead exposure — had probably limited the defendant's ability to appreciate the wrongfulness of his acts. He was spared the death penalty and given life imprisonment.

This case highlights two competing perspectives on the application of reductionist neuroscience knowledge to the practical, life-or-death issue of criminal responsibility. If an individual is burdened early in life with biological and social risk factors beyond their control which, in a probabilistic fashion, increases the likelihood of a criminal lifestyle, are they fully responsible for their homicidal actions? Conversely, all behavior has a cause that is founded in the brain. Just because a putative causal path has been documented, should it be exculpatory? Would such exculpation erode our concept of moral responsibility?



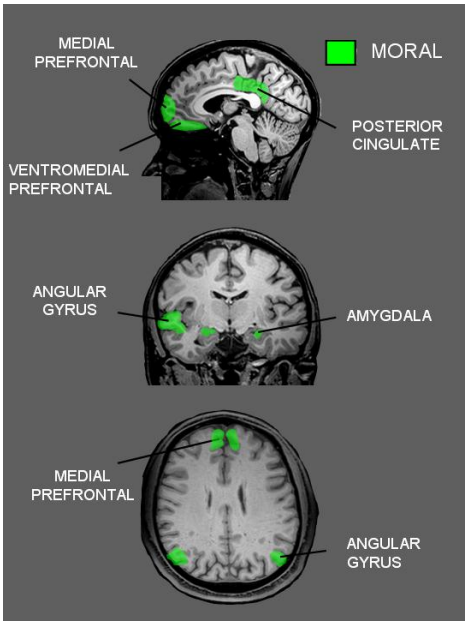
Box 3 figure. The brain scan of Donta Page, left, shows the reduced functioning of the ventral prefrontal cortex—the area of the brain that helps regulate emotions and control impulses—compared to a normal brain, right.

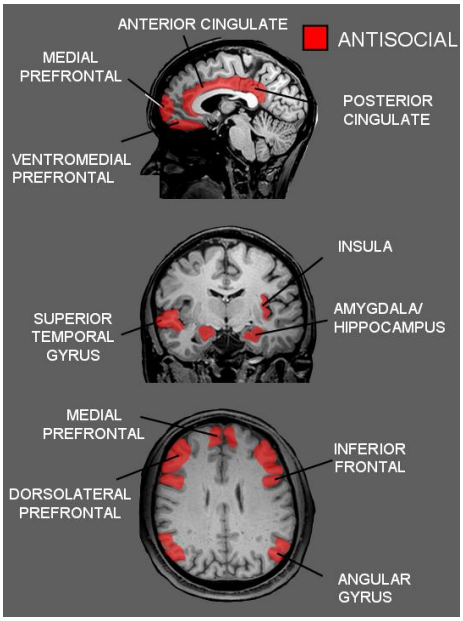
Box 4. Common neural circuits to both moral decision-making and antisocial behavior

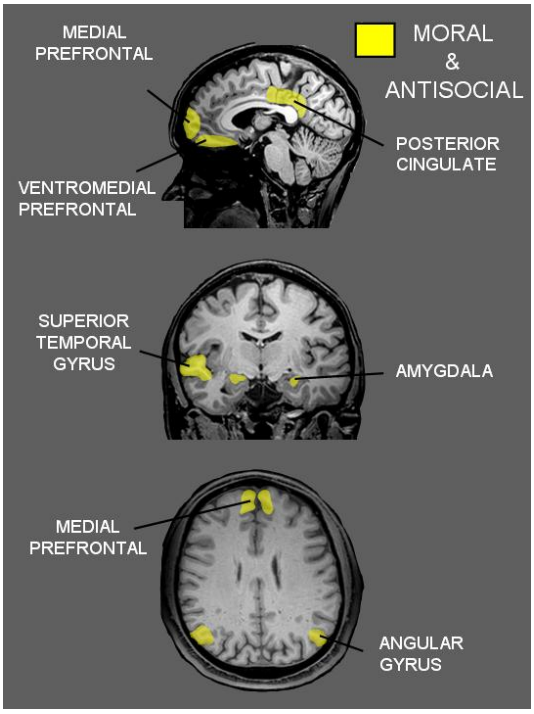
Although criminal offending is heterogeneous in nature, a common denominator is that it is immoral. It is conceivable that the neural circuitry underlying moral decision-making is impaired in offenders. This moral neural circuit is broadly comprised of the polar and medial PFC, ventral PFC, angular gyrus, posterior cingulate and amygdala. These brain regions have substantial overlap with those regions found to be structurally or functionally impaired in offenders[122] (Figure 3). This overlap gives rise to the 'neuromoral hypothesis' of antisocial behavior that *some* of the brain impairments observed in antisocial individuals disrupt moral emotion and/or decision-making, in turn predisposing to rule-breaking, antisocial behavior[1].

This raises an intriguing forensic question. There is little doubt that most violent psychopaths *know* the difference between right and wrong – but do they have the *feeling* of what is right and wrong? Moral decision-making is viewed as significantly influenced by affect[68, 94]. This 'moral feeling', centered in part on the amygdala, is argued to be the engine that translates the cognitive recognition that an act is immoral into behavioral inhibition, a mechanism that functions less well in affectively-blunted antisocial individuals. Impairments to the emotional component that comprises the feeling of what is moral is viewed as a core feature of psychopaths and is also present in other offenders.

Thus, if a criminal offender has documented disruption to this moral neural circuitry, and lacks the feeling for what is right and wrong, are they fully accountable for their immoral behavior? If this moral circuitry can be better delineated and quantified at the individual level in future years, this affective metric could be entered as a mitigating factor in the punishment phase of a trial just as low IQ — a cognitive metric — is currently used to establish lack of rational capacity and to excuse the defendant in the guilt phase of a trial.







Box 4 figure. A schematic diagram of brain regions impaired only in antisocial groups (red), activated only in moral decision-making (green) and regions common to both antisocial behavior and moral decision-making (yellow).

References

1. Raine, A. The Anatomy of Violence: The Biological Roots of Crime (Pantheon, New York, 2013).
2. Tuvblad, C. et al. The genetic and environmental etiology of decision-making: a longitudinal twin study. *J Adolesc* **36**, 245-55 (2013).
3. Ferguson, C.J. Genetic contributions to antisocial personality and behavior: a meta-analytic review from an evolutionary perspective. *J Soc Psychol* **150**, 160-80 (2010).
4. Cadoret, R.J. et al. Associations of the serotonin transporter promoter polymorphism with aggressivity, attention deficit, and conduct disorder in an adoptee population. *Compr Psychiatry* **44**, 88-101 (2003).
5. DeLisi, M., Beaver, K.M., Vaughn, M.G. & Wright, J.P. All in the Family: Gene × Environment Interaction Between DRD2 and Criminal Father Is Associated With Five Antisocial Phenotypes. *Criminal Justice and Behavior* **36**, 1187-1197 (2009).
6. DeYoung, C.G. et al. Variation in the catechol-O-methyltransferase Val(158)Met polymorphism associated with conduct disorder and ADHD symptoms, among adolescent male delinquents. *Psychiatric Genetics* **20**, 20-24 (2010).
7. Gadow, K.D., Devincent, C.J., Olvet, D.M., Pisarevskaya, V. & Hatchwell, E. Association of DRD4 polymorphism with severity of oppositional defiant disorder, separation anxiety disorder and repetitive behaviors in children with autism spectrum disorder. *Eur J Neurosci* **32**, 1058-65 (2010).
8. Vassos, E., Collier, D.A. & Fazel, S. Systematic meta-analyses and field synopsis of genetic association studies of violence and aggression. *Mol Psychiatry* (2013).
9. Caspi, A. et al. Role of genotype in the cycle of violence in maltreated children. *Science* **297**, 851-854 (2002).
10. Tremblay, R.E. Understanding development and prevention of chronic physical aggression: Towards experimental epigenetics studies. *Philosophical Transactions of the Royal Society B* **363**, 2613-2622 (2008).
11. Raine, A., Buchsbaum, M.S. & Lacasse, L. Brain abnormalities in murderers indicated by positron emission tomography. *Biological Psychiatry* **42**, 495-508 (1997).
12. Arseneault, L., Tremblay, R.E., Boulerice, B., Seguin, J.R. & Saucier, J.F. Minor physical anomalies and family adversity as risk factors for violent delinquency in adolescence. *American Journal of Psychiatry* **157**, 917-923 (2000).
13. Mednick, S.A. & Kandel, E.S. Congenital determinants of violence. *Bull Am Acad Psychiatry Law* **16**, 101-9 (1988).
14. Ryan, S.R., Schechter, J.C. & Brennan, P.A. Perinatal factors, parenting behavior, and reactive aggression: does cortisol reactivity mediate this developmental risk process? *J Abnorm Child Psychol* **40**, 1211-22 (2012).
15. Pine, D.S., Shaffer, D., Schonfeld, I.S. & Davies, M. Minor physical anomalies: modifiers of environmental risks for psychiatric impairment? *J Am Acad Child Adolesc Psychiatry* **36**, 395-403 (1997).
16. Raine, A., Lee, L., Yang, Y. & Colletti, P. Neurodevelopmental marker for limbic maldevelopment in antisocial personality disorder and psychopathy. *The British Journal of Psychiatry* **197**, 186-192 (2010).
17. Sarwar, M. The septum pellucidum: normal and abnormal. *AJNR Am J Neuroradiol* **10**, 989-1005 (1989).

18. Pardini, D.A., Raine, A., Erickson, K. & Loeber, R. Lower Amygdala Volume in Men Is Associated with Childhood Aggression, Early Psychopathic Traits, and Future Violence. *Biol Psychiatry* (2013).
19. Brennan, P.A., Grekin, E.R. & Mednick, S.A. Maternal smoking during pregnancy and adult male criminal outcomes. *Archives of General Psychiatry* **56**, 215-219 (1999).
20. Sood, B. et al. Prenatal alcohol exposure and childhood behavior at age 6 to 7 years: I. dose-response effect. *Pediatrics* **108**, E34 (2001).
21. Maughan, B., Taylor, A., Caspi, A. & Moffitt, T.E. Prenatal smoking and early childhood conduct problems. *Archives of General Psychiatry* **61**, 836-843 (2004).
22. Jaffee, S.R., Strait, L.B. & Odgers, C.L. From correlates to causes: can quasi-experimental studies and statistical innovations bring us closer to identifying the causes of antisocial behavior? *Psychol Bull* **138**, 272-95 (2012).
23. Olympio, K.P.K., Gonçalves, C., Günther, W.M.R. & Bechara, E.J.H. Neurotoxicity and aggressiveness triggered by low-level lead in children: a review. *Revista Panamericana de Salud Pública* **26**, 266-275 (2009).
24. Wright, J.P. et al. Association of prenatal and childhood blood lead concentrations with criminal arrests in early adulthood. *Plos Medicine* **5**, 732-740 (2008).
25. Fergusson, D.M., Boden, J.M. & Horwood, L.J. Dentine lead levels in childhood and criminal behaviour in late adolescence and early adulthood. *J Epidemiol Community Health* **62**, 1045-50 (2008).
26. Ericson, J.E. et al. Prenatal manganese levels linked to childhood behavioral disinhibition. *Neurotoxicol Teratol* **29**, 181-7 (2007).
27. Neugebauer, R., Hoek, H.W. & Susser, E. Prenatal exposure to wartime famine and development of antisocial personality disorder in early adulthood. *Jama-Journal of the American Medical Association* **282**, 455-462 (1999).
28. Galler, J.R. et al. Socioeconomic outcomes in adults malnourished in the first year of life: a 40-year study. *Pediatrics* **130**, e1-7 (2012).
29. Liu, J.H., Raine, A., Venables, P.H. & Mednick, S. Malnutrition at age 3 years and externalizing behavior problems at ages 8, 11 and 17 years. *American Journal of Psychiatry* **161**, 2005-2013 (2004).
30. Hawes, D.J., Brennan, J. & Dadds, M.R. Cortisol, callous-unemotional traits, and pathways to antisocial behavior. *Curr Opin Psychiatry* **22**, 357-62 (2009).
31. van Goozen, S.H., Fairchild, G., Snoek, H. & Harold, G.T. The evidence for a neurobiological model of childhood antisocial behavior. *Psychol Bull* **133**, 149-82 (2007).
32. Shoal, G.D., Giancola, P.R. & Kilrillova, G.P. Salivary cortisol, personality, and aggressive behavior in adolescent boys: a 5-year longitudinal study. *Child and Adolescent Psychiatry and Mental Health* **42**, 1101-1107 (2003).
33. McBurnett, K., Lahey, B.B., Rathouz, P.J. & Loeber, R. Low salivary cortisol and persistent aggression in boys referred for disruptive behavior. *Archives of General Psychiatry* **57**, 38-43 (2000).
34. Archer, J., Graham-Kevan, N. & Davies, M. Testosterone and aggression: A reanalysis of Book, Starzyk, and Quinsey's (2001) study. *Aggression and Violent Behavior* **10**, 241-261 (2005).

35. Pope, H.G., Jr, Kouri, E.M. & Hudson, J.I. Effects of supraphysiologic doses of testosterone on mood and aggression in normal men: A randomized controlled trial. *Archives of General Psychiatry* **57**, 133-140 (2000).
36. O'Connor, D.B., Archer, J., Hair, W.M. & Wu, F.C. Exogenous testosterone, aggression, and mood in eugonadal and hypogonadal men. *Physiol Behav* **75**, 557-66 (2002).
37. Tarter, R.E. et al. Prospective study of the association between abandoned dwellings and testosterone level on the development of behaviors leading to cannabis use disorder in boys. *Biol Psychiatry* **65**, 116-21 (2009).
38. van Bokhoven, I. et al. Salivary testosterone and aggression, delinquency, and social dominance in a population-based longitudinal study of adolescent males. *Hormones and Behavior* **50**, 118-125 (2006).
39. Nelson, R.J. & Trainor, B.C. Neural mechanisms of aggression. *Nat Rev Neurosci* **8**, 536-546 (2007).
40. Moore, T.M., Scarpa, A. & Raine, A. A meta-analysis of serotonin metabolite 5-HIAA and antisocial behavior. *Aggressive Behavior* **28**, 299-316 (2002).
41. Coccaro, E.F. Central serotonin and impulsive aggression. *Br J Psychiatry Suppl*, 52-62 (1989).
42. Rubia, K. et al. Tryptophan depletion reduces right inferior prefrontal activation during response inhibition in fast, event-related fMRI. *Psychopharmacology (Berl)* **179**, 791-803 (2005).
43. Blair, R.J. The amygdala and ventromedial prefrontal cortex in morality and psychopathy. *Trends in Cognitive Sciences* **11**, 387-392 (2007).
44. Alia-Klein, N. et al. Brain monoamine oxidase A activity predicts trait aggression. *J Neurosci* **28**, 5099-104 (2008).
45. Ortiz, J. & Raine, A. Heart rate level and antisocial behavior in children and adolescents: A meta-analysis. *Journal of the American Academy of Child and Adolescent Psychiatry* **43**, 154-162 (2004).
46. Armstrong, T.A., Keller, S., Franklin, T.W. & Macmillan, S.N. Low Resting Heart Rate and Antisocial Behavior: A Brief Review of Evidence and Preliminary Results From a New Test. *Criminal Justice and Behavior* **36**, 1125-1140 (2009).
47. De Vries-Bouw, M. et al. The predictive value of low heart rate and heart rate variability during stress for reoffending in delinquent male adolescents. *Psychophysiology* **48**, 1597-604 (2011).
48. Jennings, W.G., Piquero, A.R. & Farrington, D.P. Does resting heart rate at age 18 distinguish general and violent offending up to age 50? Findings from the Cambridge Study in Delinquent Development. *Journal of Criminal Justice* **41**, 213-219 (2013).
49. Raine, A., Venables, P.H. & Williams, M. Relationships between central and autonomic measures of arousal at age 15 years and criminality at age 24 years. *Archives of General Psychiatry* **47**, 1003-1007 (1990).
50. Gao, Y. & Raine, A. P3 event-related potential impairments in antisocial and psychopathic individuals: A meta-analysis. *Biological Psychology* **82**, 199-210 (2009).
51. Gao, Y., Raine, A., Venables, P.H. & Mednick, S.A. The Association Between P3 Amplitude at Age 11 and Criminal Offending at Age 23. *Journal of Clinical Child & Adolescent Psychology* **42**, 120-130 (2012).
52. Lorber, M.F. Psychophysiology of Aggression, Psychopathy, and Conduct Problems: A Meta-Analysis. *Pychological Bulletin* **130**, 531-552 (2004).

53. Raine, A. The psychopathology of crime: Criminal behavior as a clinical disorder (Academic Press, San Diego, CA, 1993).
54. Fairchild, G., Van Goozen, S.H., Stollery, S.J. & Goodyer, I.M. Fear conditioning and affective modulation of the startle reflex in male adolescents with early-onset or adolescence-onset conduct disorder and healthy control subjects. *Biol Psychiatry* **63**, 279-85 (2008).
55. Fairchild, G., Stobbe, Y., van Goozen, S.H.M., Calder, A.J. & Goodyer, I.M. Facial Expression Recognition, Fear Conditioning, and Startle Modulation in Female Subjects with Conduct Disorder. *Biological psychiatry* **68**, 272-279 (2010).
56. Syngelaki, E.M., Fairchild, G., Moore, S.C., Savage, J.C. & van Goozen, S.H. Fearlessness in juvenile offenders is associated with offending rate. *Dev Sci* **16**, 84-90 (2013).
57. Sehlmeyer, C. et al. Human fear conditioning and extinction in neuroimaging: a systematic review. *PLoS One* **4**, e5865 (2009).
58. Patrick, C.J., Venables, N.C. & Skeem, J. in Psychopathy and Law: A Practitioner's Guide (eds. Häkkänen-Nyholm, H. & Nyholm, J.-O.) 39-77 (Wiley, Chichester, UK, 2012).
59. Gao, Y., Raine, A., Venables, P.H. & Dawson, M.E. Association of poor childhood fear conditioning and adult crime. *American Journal of Psychiatry* **167**, 56-60 (2010).
60. Raine, A., Venables, P.H. & Williams, M. Better autonomic conditioning and faster electrodermal half-recovery time at age 15 years as possible protective factors agains crime at 29 years. *Developmental Psychology* **32**, 624-630 (1996).
61. Yang, Y. & Raine, A. Prefrontal structural and functional brain imaging findings in antisocial, violent, and psychopathic individuals: a meta-analysis. *Psychiatry Research* **174**, 81-88 (2009).
62. Holroyd, C.B. & Coles, M.G.H. The neural basis. of human error processing: Reinforcement learning, dopamine, and the error-related negativity. *Psychological Review* **109**, 679-709 (2002).
63. Kiehl, K.A., Liddle, P.F. & Hopfinger, J.B. Error processing and the rostral anterior cingulate: an event-related fMRI study. *Psychophysiology* **37**, 216-223 (2000).
64. Kosson, D.S. et al. The role of the amygdala and rostral anterior cingulate in encoding expected outcomes during learning. *Neuroimage* **29**, 1161-72 (2006).
65. Devinsky, O., Morrell, M.J. & Vogt, B.A. Contributions of anterior cingulate cortex to behaviour. *Brain* **118 (Pt 1)**, 279-306 (1995).
66. Danckert, J. et al. Goal-directed selective attention and response competition monitoring: evidence from unilateral parietal and anterior cingulate lesions. *Neuropsychology* **14**, 16-28 (2000).
67. Hornak, J. et al. Changes in emotion after circumscribed surgical lesions of the orbitofrontal and cingulate cortices. *Brain* **126**, 1691-1712 (2003).
68. Damasio, A.R. Descartes' error: Emotion, reason, and the human brain (GP Putnam's Sons, New York, 1994).
69. Blair, R.J. The roles of the orbital frontal cortex in the modulation of antisocial behavior. *Brain and Cognition* **55**, 198-208 (2004).
70. Grafman, J. et al. Frontal lobe injuries, violence, and aggression: a report of the Vietnam Head Injury Study. *Neurology* **46**, 1231-8 (1996).

71. Burns, J.M. & Swerdlow, R.H. Right orbitofrontal tumor with pedophilia symptom and constructional apraxia sign. *Archives of Neurology* **60**, 437-440 (2003).
72. Yang, Y., Raine, A., Narr, K.L., Colletti, P. & Toga, A.W. Localization of deformations within the amygdala in individuals with psychopathy. *Archives of General Psychiatry* **66**, 986-994 (2009).
73. Glenn, A.L., Raine, A. & Schug, R.A. The neural correlates of moral decision-making in psychopathy. *Molecular Psychiatry* **14**, 5-6 (2009).
74. Jones, A.P., Laurens, K.R., Herba, C.M., Barker, G.J. & Viding, E. Amygdala hypoactivity to fearful faces in boys with conduct problems and callous-unemotional traits. *American Journal of Psychiatry* **166**, 95-102 (2009).
75. Birbaumer, N. et al. Deficient fear conditioning in psychopathy: a functional magnetic resonance imaging study. *Archives of General Psychiatry* **62**, 799-805 (2005).
76. Coccaro, E.F., McCloskey, M.S., Fitzgerald, D.A. & Phan, K.L. Amygdala and orbitofrontal reactivity to social threat in individuals with impulsive aggression. *Biological Psychiatry* **62**, 168-178 (2007).
77. Tranel, D., Gullickson, G., Koch, M. & Adolphs, R. Altered experience of emotion following bilateral amygdala damage. *Cognitive Neurospsychiatry* **11**, 219-232 (2006).
78. Adolphs, R. et al. Recognition of facial emotion in nine individuals with bilateral amygdala damage. *Neuropsychologia* **37**, 1111-1117 (1999).
79. Aharoni, E. et al. Neuroprediction of future rearrest. *Proceedings of the National Academy of Sciences* **110**, 6223-6228 (2013).
80. Fazel, S., Lichtenstein, P., Grann, M. & Långström, N. Risk of violent crime in individuals with epilepsy and traumatic brain injury: a 35-year Swedish population study. *PLoS Med* **8**, e1001150 (2011).
81. Timonen, M. et al. The association of preceding traumatic brain injury with mental disorders, alcoholism and criminality: the Northern Finland 1966 Birth Cohort Study. *Psychiatry Res* **113**, 217-26 (2002).
82. Raine, A. et al. Increased executive functioning, attention, and cortical thickness in white-collar criminals. *Hum Brain Mapp* **33**, 2932-40 (2012).
83. Toro, R. et al. Prenatal exposure to maternal cigarette smoking and the adolescent cerebral cortex. *Neuropsychopharmacology* **33**, 1019-27 (2008).
84. Cecil, K.M. et al. Decreased brain volume in adults with childhood lead exposure. *Plos Medicine* **5**, 741-750 (2008).
85. Meyer-Lindenberg, A. et al. Neural mechanisms of genetic risk for impulsivity and violence in humans. *Proceedings of the National Academy of Sciences of the United States of America* **103**, 6269-6274 (2006).
86. Wahlund, K. & Kristiansson, M. Aggression, psychopathy and brain imaging - Review and future recommendations. *International Journal of Law and Psychiatry* **32**, 266-271 (2009).
87. Cornet, L.J.M., de Kogel, C.H., Nijman, H.L.I., Raine, A. & van der Laan, P.H. Neurobiological Factors as Predictors of Cognitive–Behavioral Therapy Outcome in Individuals With Antisocial Behavior: A Review of the Literature. *International Journal of Offender Therapy and Comparative Criminology* (2013).
88. Tiger Aspect Productions. Mindshock: Sex on the Brain. Channel Four UK.
89. Morse, S.J. Voluntary control of behavior and responsibility. *Am J Bioeth* **7**, 12-3 (2007).
90. Morse, S.J. Psychopathy and criminal responsibility. *Neuroethics* **1**, 205-212 (2008).

91. Viding, E. & McCrory, E.J. Genetic and neurocognitive contributions to the development of psychopathy. *Development and Psychopathology* **24**, 969-983 (2012).
92. Hare, R.D. & Neumann, C.S. Structural models of psychopathy. *Curr Psychiatry Rep* **7**, 57-64 (2005).
93. van der Leij, J.B., Jackson, J.L., Malsch, M. & Nijboer, J.F. Residential mental health assessment within Dutch criminal cases: a discussion. *Behav Sci Law* **19**, 691-702 (2001).
94. Greene, J.D., Sommerville, R.B., Nystrom, L.E., Darley, J.M. & Cohen, J. An fMRI investigation of emotional engagement in moral judgment. *Science* **293**, 2105-2108 (2001).
95. Neumann, C.S., Johansson, P.T. & Hare, R.D. The Psychopathy Checklist-Revised (PCL-R), low anxiety, and fearlessness: a structural equation modeling analysis. *Personal Disord* **4**, 129-37 (2013).
96. Patrick, C.J., Cuthbert, B.N. & Lang, P.J. Emotion in the criminal psychopath: fear image processing. *Journal of Abnormal Psychology* **103**, 523-534 (1994).
97. Sapolsky, R.M. The frontal cortex and the criminal justice system. *Philos Trans R Soc Lond B Biol Sci* **359**, 1787-96 (2004).
98. Farah, M.J. Neuroethics: the ethical, legal, and societal impact of neuroscience. *Annu Rev Psychol* **63**, 571-91 (2012).
99. Frazer, K.A., Murray, S.S., Schork, N.J. & Topol, E.J. Human genetic variation and its contribution to complex traits. *Nat Rev Genet* **10**, 241-51 (2009).
100. Hariri, A.R. The neurobiology of individual differences in complex behavioral traits. *Annual Review of Neuroscience* **32**, 225-247 (2009).
101. Raine, A. et al. Corpus Callosum Abnormalities in Psychopathic Antisocial Individuals. *Archives of General Psychiatry* **60**, 1134-1142 (2003).
102. Raine, A., Lencz, T., Bihrle, S., LaCasse, L. & Colletti, P. Reduced prefrontal gray matter volume and reduced autonomic activity in antisocial personality disorder. *Archives of General Psychiatry* **57**, 119-127 (2000).
103. Society, T.R. (London, 2011).
104. Berk, R., Sherman, L., Barnes, G., Kurtz, E. & Ahlman, L. Forecasting murder within a population of probationers and parolees: a high stakes application of statistical learning. *Journal of the Royal Statistical Society: Series A (Statistics in Society)* **172**, 191-211 (2009).
105. Pappadopulos, E. et al. Pharmacotherapy of aggression in children and adolescents: efficacy and effect size. *J Can Acad Child Adolesc Psychiatry* **15**, 27-39 (2006).
106. New, A.S. et al. Fluoxetine increases relative metabolic rate in prefrontal cortex in impulsive aggression. *Psychopharmacology (Berl)* **176**, 451-8 (2004).
107. Lösel, F. & Schmucker, M. The effectiveness of treatment for sexual offenders: A comprehensive meta-analysis. *Journal of Experimental Criminology* **1**, 117-146 (2005).
108. Douglas, T., Bonte, P., Focquaert, F., Devolder, K. & Sterckx, S. Coercion, Incarceration, and Chemical Castration: An Argument From Autonomy. *Journal of Bioethical Inquiry*, 1-13 (2013).
109. Zaalberg, A., Nijman, H., Bulten, E., Stroosma, L. & van der Staak, C. Effects of Nutritional Supplements on Aggression, Rule-Breaking, and Psychopathology Among Young Adult Prisoners. *Aggressive Behavior* **36**, 117-126 (2010).

110. Gesch, S.M., Hampson, S.E., Eves, A. & Crowder, M.J. Influence of supplemental vitamins, minerals and essential fatty acids on the antisocial behaviour of young adult prisoners. *British Journal of Psychiatry* **181**, 22-28 (2002).
111. Gustafsson, P.A. et al. EPA supplementation improves teacher-rated behaviour and oppositional symptoms in children with ADHD. *Acta Paediatr* **99**, 1540-9 (2010).
112. Kirby, A., Woodward, A., Jackson, S., Wang, Y. & Crawford, M.A. A double-blind, placebo-controlled study investigating the effects of omega-3 supplementation in children aged 8-10 years from a mainstream school population. *Res Dev Disabil* **31**, 718-30 (2010).
113. Calderon, F. & Kim, H.-Y. Docosahexaenoic acid promotes neurite growth in hippocampal neurons. *Journal of Neurochemistry* **90**, 979-988 (2004).
114. Olds, D. et al. Long-term effects of nurse home visitation on children's criminal and antisocial behavior: 15-year follow-up of a randomized controlled trial. *Journal of the American Medical Association* **280**, 1238-1244 (1998).
115. Raine, A., Mellingen, K., Liu, J., Venables, P.H. & Mednick, S. Effects of environmental enrichment at 3-5 years on schizotypal personality and antisocial behavior at ages 17 and 23 years. *American Journal of Psychiatry* **160**, 1627-1635 (2003).
116. Ruff, C.C., Ugazio, G. & Fehr, E. Changing Social Norm Compliance With Noninvasive Brain Stimulation. *Science* (2013).
117. Desbordes, G. et al. Effects of mindful-attention and compassion meditation training on amygdala response to emotional stimuli in an ordinary, non-meditative state. *Frontiers in Human Neuroscience* **6** (2012).
118. Davidson, R.J. et al. Alterations in Brain and Immune Function Produced by Mindfulness Meditation. *Psychosomatic Medicine* **65**, 564-570 (2003).
119. Himelstein, S. Meditation Research: The State of the Art in Correctional Settings. *International Journal of Offender Therapy and Comparative Criminology* (2010).
120. Wupperman, P. et al. Mindfulness and modification therapy for behavioral dysregulation: results from a pilot study targeting alcohol use and aggression in women. *J Clin Psychol* **68**, 50-66 (2012).
121. Hjalmarsson, R. & Lindquist, M.J. The origins of intergenerational associations in crime: Lessons from Swedish adoption data. *Labour Economics* **20**, 68-81 (2013).
122. Raine, A. & Yang, Y. Neural foundations to moral reasoning and antisocial behavior. *Social, Cognitive, and Affective Neuroscience* **1**, 203-213 (2006).