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The neurobiology of psychopathic traits in youths

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Abstract

Conduct disorder is a childhood behaviour disorder that is characterized by persistent aggressive or antisocial behaviour that disrupts the child's environment and impairs his or her functioning. A proportion of children with conduct disorder have psychopathic traits. Psychopathic traits consist of a callous–unemotional component and an impulsive–antisocial component, which are associated with two core impairments. The first is a reduced empathic response to the distress of other individuals, which primarily reflects reduced amygdala responsiveness to distress cues; the second is deficits in decision making and in reinforcement learning, which reflects dysfunction in the ventromedial prefrontal cortex and striatum. Genetic and prenatal factors contribute to the abnormal development of these neural systems, and social–environmental variables that affect motivation influence the probability that antisocial behaviour will be subsequently displayed.

Aggressive and antisocial behaviours are the leading cause of child and adolescent referrals to mental health clinicians and can lead to a diagnosis of conduct disorder¹. However, not all patients receiving this diagnosis show the same pathophysiology. One form of conduct disorder is marked by the presence of psychopathic traits and will be the main focus of this Review. Psychopathic traits have a core callous–unemotional component (for example, lack of guilt and empathy) and an impulsive–antisocial component². They are detectable early in childhood and persist into adulthood^{3,4}. Clinically, understanding psychopathic traits is important, as their presence can interfere with socialization⁵ and currently available conduct-disorder treatments^{6,7}.

There has been rapid progress in our understanding of the neurobiology of psychopathic traits, particularly the callous–unemotional component, over the past 5 years. Indeed, partly as a result of neurobiological studies^{8–10} a form of callous–unemotional specifier (termed 'limited prosocial emotions') has been introduced to the conduct disorder diagnosis in the fifth edition of the *Diagnostic and Statistical Manual (DSM-5)*¹¹. To qualify for this specifier, an individual must have displayed two of four characteristics in the previous 12 months in multiple settings. These characteristics are lack of remorse or guilt; callousness (that is, lack of empathy); lack of concern about performance (for example, at school); and shallow or deficient affect (a lack of expression of feelings to others). A different form of

conduct disorder is associated with increased risk of mood and anxiety disorders and emotional lability (BOX 1).

This Review discusses why psychopathic traits in youths are associated with an increased risk of antisocial behaviour and aggression. I use a cognitive neuroscience approach; that is, I consider how specific functional impairments in specific neural systems give rise to the development of psychopathic traits. I then use cognitive neuroscience findings to interpret both data on genetic and environmental risk factors for aggression and data on potential treatment possibilities. Finally, I present an integrative model of psychopathic traits, conduct disorder and aggression more generally.

A cognitive neuroscience approach

Youths with psychopathic traits show two main cognitive impairments. The first is a specific form of empathic dysfunction. Indeed, the clinical literature has long associated psychopathy with empathy impairment^{12,13}. However, the term empathy subsumes two critical processes that are distinct at both the cognitive and the neural level¹⁴: cognitive empathy involves the representation of the intentions and thoughts of other individuals (also known as theory of mind)¹⁵, whereas emotional empathy involves affective responses to emotional displays of other individuals and to verbal descriptions of the emotional states of other individuals. Psychopathic traits are not associated with reductions in cognitive empathy but they — and particularly the callous–unemotional component — are associated with reductions in specific forms of emotional empathy (in particular, responding to the fear, sadness, pain and happiness of others). This functional impairment is associated with reduced amygdala and ventromedial prefrontal cortex (vmPFC) responsiveness to distress cues (FIG. 1).

The second cognitive impairment in youths with psychopathic traits is impairment in aspects of decision making, specifically in reinforcement learning and the representation of reinforcement expectancies. This impairment may relate more to the impulsive–antisocial component of psychopathic traits and is also seen, at least partially, in patients with other externalizing disorders, such as attention-deficit hyperactivity disorder (ADHD), and in those at risk of developing drug addiction. This functional impairment is associated with dysfunction in the vmPFC and striatum (FIG. 1).

Cognitive empathy

It has been known for some time that adults with psychopathic traits show no impairment in cognitive empathy^{16–18}. This finding has been replicated recently in adolescents with psychopathic traits^{19,20}. A recent functional MRI (fMRI) study examined participants who were using information about the intentions and beliefs of other individuals to predict their behaviour²¹. This study demonstrated that youths with psychopathic traits show normal recruitment of the medial frontal cortex (including the vmPFC), temporal parietal junction, posterior cingulate cortex and temporal pole when engaged in this cognitive empathy task. These are all regions that have been implicated in cognitive empathy in healthy individuals^{22–24}.

Emotional empathy

Empathic reactions can be evoked by facial cues, auditory cues, body postures and even text. Emotional empathy has a communicatory function: the emotional cues of others impart specific information to the observer^{25,26}, and emotional empathy is the observer's 'translation' of this communication. It has been argued that different facial expressions provide different communicatory signals, initiate different forms of reinforcement-based learning and are processed by neural systems that are at least partially distinct²⁵.

The emotional empathy impairment in youths (and adults) with psychopathic traits is selective. For example, they have normal recognition of expressions of anger and disgust (for meta-analytic reviews of the literature, see REFS 27,28), and blood oxygen level-dependent (BOLD) responses to angry expressions are similar to those in typically developing adolescents (the response to disgust expressions has not been tested)^{8,29,30}. By contrast, they display impaired processing of both distress cues (that is, expressions of fear, sadness or pain) and happy expressions; studies quite consistently show impaired recognition of fearful and, to a lesser extent, sad and happy expressions in youths (and adults) with psychopathic traits^{31–36}. These findings have been confirmed in recent meta-analytic reviews of the literature^{27,28}. The impaired recognition of fearfulness and sadness also applies to vocal tones^{35,37} and body postures³⁸. In addition, youths with psychopathic traits show reduced autonomic responses to fearful and sad expressions and pain in other individuals, as well as atypical electroencephalography responses to pain in others^{39–43}. In line with findings of reduced responsiveness to the distress of others, children with high callous–unemotional traits state that they are less concerned (relative to children with low callous–unemotional traits) that aggressive behaviour will result in suffering in the victim⁴⁴. Importantly, although youths with psychopathic traits show a reduced response to emotional stimuli (whether indexed by autonomic or amygdala activity), the response is not absent, and increasing the intensity of an emotional stimulus — through morphing³¹ or by orientating the participant's attention towards the eyes — reduces or removes group differences in fearful expression recognition^{34,45}.

In healthy individuals, amygdala activation by distress cues leads to both increased arousal (via projections to the brainstem) and increased attention to these cues. This increased attention reflects the reciprocal connections between the amygdala and temporal cortex, such that amygdala activity will stimulate the neurons that represent the emotionally salient features of the eliciting cue, further strengthening the representation of these features and increasing the probability that they will 'win' the competition for representation⁴⁶. In the case of fearful expressions, the eye region is a particularly emotionally salient feature⁴⁷ and representation of the eyes will thus be particularly strengthened when a healthy individual sees a fearful face. As a result of stimulus-reinforcement learning, an association is formed between the 'social punishment' of the fearful or sad facial expression and any representations of objects or actions associated with this expression. Which object is associated will be specified by the expresser's eye gaze²⁹.

The deficits in emotional empathy shown by adolescents with psychopathic traits involve amygdala dysfunction³¹. Indeed, fMRI studies in adolescents with psychopathic traits have consistently shown reduced amygdala responses to images of faces with fearful

expressions^{8,10,30,48,49}. Furthermore, youths with conduct disorder who have psychopathic traits show reduced amygdala and rostral medial frontal cortical responses to images of other individuals in pain^{47,50}. The impaired recognition of happy expressions may also relate to amygdala dysfunction, but this has not yet been empirically confirmed. It is the callous–unemotional component of psychopathic traits that seems to be particularly associated with the reduced amygdala response to distress cues^{10,48}.

Appropriate processing of distress cues is critical for socialization. Many studies in humans and animals have shown the role of emotional expressions in the transmission of the value of actions and objects. For example, humans value positively those actions and objects that make care-givers smile and avoid actions and objects for which care-givers show fear^{51,52}. Similarly, individuals approach objects associated with happiness in another individual and avoid objects associated with fear or disgust in another individual. The amygdala allows the association of the stimulus (the object or action towards which the expression was displayed) with the reinforcement (the expression itself), so that the object or action becomes associated with a value⁵³. Indeed, recent animal studies have confirmed a critical role for the amygdala in observational fear⁵⁴. In individuals with psychopathic traits, reduced processing of distress cues by the amygdala would lead to reduced aversion for actions that harm others, so that the individual is more likely to commit actions that harm others to achieve their goals (BOX 2).

Emotional empathy also has a communicatory function: it is critical for learning the social value of actions and objects and important for appropriate decision making. In healthy individuals, the strength of the representation of the distress of the victim is inversely related to the probability of an aggressive response⁵⁵. Brain regions that are important for representing the valence of objects and actions and for using this information to guide choices towards or away from these objects and actions include the vmPFC and anterior insular cortex (see below)^{56–59}. Furthermore, there is considerable evidence, including from lesion studies, that the vmPFC and insular cortex are critical for empathic responding^{60–63}. Youths with conduct disorder show reduced rostral vmPFC activation in response to observing pain in other individuals⁵⁰, as well as reduced insula responses when using emotional reactions from other individuals to predict the subsequent behaviour of these individuals²¹. In both cases, the activity reduction in these areas was correlated with the severity of psychopathic⁵⁰ or callous–unemotional²¹ traits.

In summary, these findings suggest that adolescents with psychopathic traits not only form weaker associations between representations of actions that harm others and the aversive consequences of these actions to other individuals but also apply this information less during decision making. Such individuals are more likely to commit actions that will harm other individuals, because they are less likely to be deterred from committing such actions by any expectations regarding the distress the action would cause in the victims.

Emotional learning and decision making

Youths with psychopathic traits show pronounced impairments in emotional learning and decision making. This reflects not only reduced responsiveness to the social reinforcers (emotional expressions) considered above but also deficits in the processes underlying

aversive conditioning, passive avoidance learning⁶⁴, operant extinction^{2,65,66} and reversal learning^{67,68}. These impairments manifest when making moral judgements⁶⁹ and in other decision-making paradigms⁷⁰. It should be noted that reduced aversive conditioning has so far been assessed and found only in adult individuals with psychopathic traits^{71,72}. However, youths with conduct disorder have also been reported to show reduced aversive conditioning⁷³, and a propensity for aversive conditioning at the age of 3 years predicts future antisocial behaviour⁷⁴.

Youths with psychopathic traits show deficits in the capacity to link outcomes (rewards or punishments) with stimuli or responses, and this is due to dysfunction within the amygdala, striatum (caudate and nucleus accumbens) and vmPFC⁷⁵. In addition, there is evidence that the use of outcome information by the anterior insula, inferior frontal cortex and dorsomedial PFC (dmPFC) to guide the individual away from suboptimal behavioural choices^{58,59} is disrupted in adolescents with psychopathic traits⁷⁶. Clinically, this impairment may manifest in many destructive behaviours: for example, deciding to mug people on the street corner on which the individual was almost arrested the night before or to fight someone in response to mild provocation (in other words, to 'be a man'), despite repeated negative consequences of such behaviours. The effective use of reinforcement outcome information during decision making requires two components. The first is the appropriate representation of the reward or punishment received when an action has been performed. Prediction error signalling is critical for this^{56,77}. Prediction error signals are thought to spur reinforcement learning (mediated by both the amygdala and striatum): the greater the prediction error, the greater the change in the reinforcement associated with the stimulus⁷⁸. The second component is the appropriate representation of the expected value when considering whether to perform an action.

The vmPFC is involved in encoding received rewards^{56,57}. Youths with psychopathic tendencies⁶⁴ and conduct disorder⁷⁹, or with increased levels of antisocial behaviour⁸⁰, show reduced vmPFC response to the receipt of a reward (although there is one report that youths with externalizing disorders show heightened responsiveness to rewards⁸¹). This is thought to reflect disrupted prediction error signalling^{9,64,76}. Many studies in healthy adults have shown that the size of the positive prediction error (when a reward is larger than expected) is correlated with activity within the striatum^{56,57}. This positive association between positive prediction errors and activity within the striatum also exists in healthy youths, but it is less strong in adolescents with psychopathic traits⁷⁶. Given the importance of prediction error signalling for initiating reinforcement learning⁷⁸, reduced prediction error signalling should result in poorer, and slower, learning of the reinforcements associated with objects and actions.

One particularly interesting feature of prediction error signalling in youths with psychopathic traits concerns their response to punishment. Punishments that are worse than expected are typically associated with a reduction in striatal activity in healthy adults and youths^{56,57}. By contrast, adolescents with psychopathic traits showed a positive relationship between prediction errors to punishment and activity within the striatum⁷⁶. This is in agreement with earlier studies that showed increased responses to unexpected punishment within the vmPFC and striatum in youths with psychopathic traits and in antisocial youths

more generally^{64,80}. The reason for these increased, as opposed to decreased, striatal and vmPFC responses to unexpected punishment remains unclear, but it probably contributes to their decision-making impairment.

The representation of expected value is also disrupted in youths with psychopathic traits. Studies have shown a positive correlation between the expected value associated with a response or a stimulus and activity within the vmPFC in healthy adults and adolescents^{56,57}. Thus, as the expected value associated with a stimulus increases (that is, the stimulus is an increasingly good predictor of reward), the individual is more likely to respond to that stimulus. By contrast, in a recent model-based fMRI study, youths with psychopathic traits showed a weaker association between expected value and both choice behaviour and vmPFC activity during choice than healthy youths⁷⁶. Thus, youths with psychopathic traits are poorer at using and representing expected value information, and this may impair their decision making.

Interestingly, healthy adolescents also show a stronger correlation between expected value and activity within the anterior insula, inferior frontal cortex and dmPFC than adolescents with psychopathic tendencies when avoiding stimuli that it would have been better to approach (because appropriate representation of expected values would predict that responding would engender reward)⁷⁶. The anterior insula, inferior frontal cortex and dmPFC have been implicated in guiding the individual away from suboptimal choices^{58,59}. Although one study suggested that the functioning of the anterior insula and dmPFC is disrupted in individuals with psychopathic traits⁸², this disruption is only partial. The recruitment of both regions is comparable to that seen in healthy youths in tests in which they are altering their behaviour in immediate response to punishment cues or during response conflict^{9,83}. As such, the reduced activity may reflect problems in the use of expected value information rather than disruption in these regions *per se*.

Notably, although youths with conduct disorder and psychopathic traits show the above deficits in decision making and its computational underpinnings, there are no clear indications that these deficits are related to the severity of psychopathic traits specifically. This is in contrast to the empathy dysfunction discussed above: repeated findings have shown that weaker responses in the amygdala, vmPFC and anterior insula to empathy cues are associated with higher severity of psychopathic traits^{8,21,48,50}. Decision-making deficits may not be specific to psychopathic traits but may also occur in individuals showing high levels of externalizing behaviour. For example, both individuals with ADHD^{84–86} and children of alcoholics, who are at risk of developing various externalizing problems, including drug addiction and conduct disorder^{87,88}, show reduced striatal activity in anticipation of rewards^{89,90}. This shared dysfunction may underpin the high comorbidity of conduct disorder with ADHD⁹¹ and substance dependence⁹².

In summary, adolescents with psychopathic traits show reduced representation of reward outcomes and expected value in the vmPFC, as well as reduced reward prediction error signalling and potentially highly atypical punishment prediction error signalling in the striatum. These computational impairments probably underlie the severe decision-making impairments seen in this population. However, these deficits (at least the reduced striatal

response to reward) are partially shared by other populations that show increased externalizing behaviour.

Structural and endocrinological findings

Structural imaging studies

Given that fMRI studies consistently show reduced activity in the amygdala in response to fearful expressions in youths with psychopathic traits, as well as aberrant striatal and vmPFC activity in youths with conduct disorder and psychopathic traits, it is worth considering whether structural abnormalities are also seen within these regions. Unfortunately, most structural imaging studies performed so far involved groups of patients with conduct disorder more generally rather than patients with psychopathic traits specifically. Nevertheless, these studies have relatively consistently reported reduced amygdala volumes^{93–97}, although two did not^{98,99}. Moreover, temporal cortex volume^{93,95,100} and thickness¹⁰¹ are reduced in youths with conduct disorder. Findings regarding the vmPFC have been mixed, with reductions in volume^{93,97}, cortical thickness¹⁰² or folding¹⁰¹ in this area reported in some studies, but not in others^{94–96,98,99}. Reduced caudate volume has only been reported three times^{95–97}, but the relative absence of such reports may reflect a lack of investigations targeting this area. In addition, and critically, a study involving over 200 incarcerated adolescents in a maximum-security facility confirmed reductions in volume, which were associated with the emotion dysfunction component of psychopathy in particular, within a large brain region that centred on the vmPFC and included the amygdala, temporal cortex and caudate⁹⁷.

The strong fMRI evidence — as well as the rather weaker structural findings — for amygdala and vmPFC abnormalities suggests a possible disruption in the uncinate fasciculus, the white-matter tract that connects the amygdala to the frontal lobe. Certainly, adults with psychopathic traits show reduced functional anisotropy of this white-matter tract^{103–105}. However, one diffusion tensor imaging study reported no fractional anisotropy difference in the uncinate fasciculus between adolescents with psychopathic traits and control youths¹⁰⁶, whereas two other studies reported an increase in fractional anisotropy in youths with conduct disorder^{107,108}. These diverging findings may reflect the development of this disorder, sample differences (for example, less severe cases in one study than in another) or the effect of past lifestyle choices in the adult samples (for example, opiate use is associated with reduced fractional anisotropy within the uncinate fasciculus¹⁰⁹).

As noted above, fMRI studies have shown that the ability of the anterior insula and dmPFC to use expected value information to guide behaviour may be compromised in adolescents with psychopathic traits⁷⁶, even if these regions respond normally to cues for response change or to response conflict^{9,83}. Structural MRI (sMRI) studies have relatively consistently reported reductions in the volume^{94,95}, thickness¹⁰² or folding¹⁰¹ of the insular cortex in youths with conduct disorder. However, it should be noted that no relationship of these reductions with psychopathic traits has been reported^{97,98}. The literature is considerably more mixed with respect to the dmPFC, with some studies^{95,101,102} but not others^{93,94,97,99} showing structural reductions in youths with conduct disorder.

Given the potential neurodevelopmental nature of psychopathic traits, it is worth noting findings on the cavum septum pellucidum (CSP) (also see BOX 3). A large CSP is a marker of abnormal brain development, particularly with regard to midline structures^{110,111}. The rapid development of the alvei of the amygdala, hippocampus, septal nuclei, fornix, corpus callosum and other midline structures is attributed to fusion of the CSP¹¹¹. Disruption in the development of these limbic structures interrupts this posterior-to-anterior fusion and leads to the preservation of the CSP. Two recent studies have reported that youths and adults with conduct problems are more likely to have a large CSP relative to that of comparison individuals^{112,113}. However, the youths sampled in this study were not selected specifically for psychopathic traits but had conduct problems more generally¹¹². These data indicate that brain maldevelopment occurs very early in (at least a substantial minority of) patients with conduct problems. However, it is important to note that an increased incidence of a large CSP is also found in patients with post-traumatic stress disorder (PTSD)¹¹⁴, schizophrenia¹¹⁵ and bipolar disorder¹¹⁶. Thus, different forms of psychopathology may be associated with an increased CSP. Alternatively, there may be a common form (or cause) of early brain maldevelopment that puts an individual at risk of a wide range of psychiatric conditions, and other environmental or genetic factors may determine which condition develops. For example, fetal exposure to alcohol and other narcotics increases the risk not only of enlarged CSP¹¹⁷ but also of aggression^{118,119} and schizophrenia¹²⁰.

In summary, sMRI findings are consistent with the fMRI findings about the amygdala and caudate in individuals with conduct disorder but rather less consistent with fMRI findings about the vmPFC. The sMRI literature also supports the idea that conduct disorder may be associated with insula dysfunction. Moreover, structural volumes of the amygdala, caudate and insula were inversely correlated with severity of psychopathic traits in a sample ($N = 296$) of incarcerated adults¹²¹. Such structural abnormalities in individuals with psychopathic traits may be common from adolescence into adulthood. By contrast, white-matter connections between the amygdala and PFC may be disturbed in adults with psychopathic traits, but this is not consistently seen in youths with psychopathic traits.

Endocrinological findings

An aberrant cortisol response in childhood has long been associated with an increased risk of antisocial behaviour¹²². However, some studies have reported increased, and others reduced, cortisol responses in antisocial populations^{123,124}. Cortisol is a peripheral marker of hypothalamus–pituitary–adrenal (HPA) axis activity — that is, of the stress response. The amygdala facilitates the activation of the HPA axis¹²⁵. Given that youths with psychopathic traits (possibly callous–unemotional traits in particular) show abnormal amygdala activity, it could be expected that antisocial adolescents with psychopathic traits show a reduced cortisol response¹²⁶. However, this prediction requires empirical investigation.

Genetic and environmental factors

Genetic factors

On the basis of the findings discussed above (and in BOX 1), one could argue that genetic variants leading to reduced amygdala responsiveness to distress cues, as well as to reduced

caudate and vmPFC responses to prediction error and expected value, should be associated with increased risk of psychopathic traits, whereas genetic variants leading to increased amygdala responsiveness to threat should be associated with an increased risk of reactive aggression¹²⁷. Indeed, findings from twin studies indicate a genetic contribution to aggression¹²⁸, and callous–unemotional traits are clearly heritable¹²⁹. However, only preliminary molecular genetic data are available. For example, one genome-wide association study generated a list of single-nucleotide polymorphisms (SNPs) that might be associated with psychopathic traits, but none of these SNPs reached genome-wide statistical significance¹³⁰. This was probably due to the relatively small sample sizes in this study (300 each of the high and low psychopathic traits groups)¹³⁰. Given the small sample sizes of most SNP studies and the lack of replications, the few results that have been obtained should be considered with caution.

Some data suggest that specific genetic polymorphisms are associated with increased amygdala responsiveness to threat. These include variants of the monoamine oxidase type A (*MAOA*) gene, a functional polymorphism in the promoter region of the serotonin transporter gene (*5-HTTLPR*; also known as *SLC6A4*) that is associated with reduced gene expression, and the Met158 variant of the catechol-*O*-methyltransferase (*COMT*) gene^{131–133}. These polymorphisms are also associated with an increased risk of aggression^{134–138}. However, these studies did not assess whether this concerns reactive (as opposed to instrumental) aggression specifically; the reasoning above (and in BOX 1) would predict this to be the case.

It is possible that variants of *MAOA*, *5-HTTLPR* and *COMT* that are associated with relatively decreased amygdala responsiveness to threat might be associated with increased risk of psychopathic traits, but few studies have investigated this. One study reported no relationship between rs4680 (Val158Met) *COMT* polymorphisms and callous–unemotional traits, although there were trend relationships between two other *COMT* SNPs and callous–unemotional traits — rs6269 (*COMT* promoter) and rs4818 (Leu136Leu)¹³⁹. Another study reported that the high-expressing genotypic variant of *5-HTTLPR*, which is associated with reduced amygdala response to threat¹⁴⁰, is also associated with increased callous–unemotional traits, but only in individuals with low family socioeconomic backgrounds¹³⁸. A recent report showed that functional SNPs of the genes encoding serotonin receptors 1B and 2A and various polymorphisms of the oxytocin receptor gene are associated with callous–emotional traits^{141,142}. However, whether these genetic variants are also associated with a reduced amygdala response to fearful expressions has yet to be determined.

In summary, although there is a genetic contribution to callous-unemotional traits, specific gene variants associated with both decreased amygdala responsiveness (that is, the neurobiological characteristic that may underpin psychopathic traits) and a generally increased risk of aggression have not yet been identified. By contrast, certain variants of *COMT*, *MAOA* and *5-HTTLPR* are associated with increased amygdala responsiveness and an increased risk of aggression (which, according to my model, would be specific for reactive aggression).

Environmental factors

The data above suggest that, similarly to genetic factors, environmental factors that lead to reduced amygdala responsiveness to distress cues should be associated with increased psychopathic traits, and that environmental factors that lead to increased amygdala responsiveness to threat should be associated with an increased risk of threat-based reactive aggression. In agreement with this, exposure to high threat levels (in the context of abuse or family violence) and/ or to neglect leads to heightened amygdala responses to threat^{143–145} and increased risk of reactive aggression¹⁴⁶.

No specific environmental factors that decrease amygdala responsiveness have yet been identified. Indeed, it has been reported that environmental factors play a smaller part than genetic factors in the high levels of aggression exhibited by youths who show callous–unemotional traits¹⁴⁷. Nevertheless, certain environmental (in particular prenatal) factors may have a role, as maternal substance abuse during pregnancy is associated with an increased likelihood of callous–unemotional traits in the child (also see BOX 3)¹⁴⁸. It is also possible that some environmental factors — interacting with specific genetic variants — result in reduced rather than increased amygdala responsiveness to emotional stimuli.

Even if environmental factors play only a small part in the pathophysiology of psychopathic traits, they clearly affect the expression of these traits. Deficits in responding to the distress of others (and in prediction error and expected value signalling) described above would give rise to an individual who is less concerned by the distress of others and makes poorer decisions. However, such deficits would not by themselves increase an individual's motivation to offend; environmental factors such as reduced socioeconomic status may do so, and exposure to criminal environments may provide the individual with behavioural repertoires. Thus, a pathophysiology such as altered amygdala responsiveness does not necessarily manifest as offending behaviour; it may only do so given certain environmental backgrounds.

Treatment implications

Conduct disorder is regarded as difficult to treat. However, there are findings that 'social and emotional learning' prevention strategies that foster the development of emotional regulation, relationship skills and responsible decision making can prevent or reduce the development of conduct problems¹⁴⁹. Similarly, psychosocial treatments such as Multidimensional Treatment Foster Care¹⁵⁰ and Multisystemic Therapy¹⁵¹ have been shown to be effective in the treatment of conduct disorder¹⁵².

However, as discussed in this Review, there are two types of conduct disorder — one associated with psychopathic traits and one associated with reactive aggression as well as mood and anxiety disorders — and they probably require different treatments. Indeed, parenting strategies that reduce conduct problems in many youths have been found to be less effective in youths with conduct problems and high levels of callous–unemotional traits relative to youths with conduct problems and low levels of callous–unemotional traits^{5,153} (but see also REF. 154). Moreover, children with callous–unemotional traits have been

found to be more resistant to psychosocial intervention than other aggressive children^{6,7,155–157}.

Given that reduced amygdala responsiveness to distress cues is associated with an increased risk of psychopathic traits, whereas increased amygdala responsiveness to threat is associated with an increased risk of threat-based reactive aggression (BOX 1), some patients may require interventions that increase amygdala responsiveness (and increase appropriate prediction error and expected value signalling during decision making), whereas others may require interventions that decrease amygdala responsiveness. Psychosocial prevention and intervention strategies can be notably effective in reducing threat sensitivity in the context of anxiety disorders. Interestingly, such treatments have been shown to reduce the heightened amygdala response to threat in patients with PTSD¹⁵⁸. Many adolescents with conduct disorder have experienced maltreatment, and co-morbidity with PTSD is high¹⁵⁹ — presumably in the subgroup that shows heightened threat sensitivity. It is thus plausible, although it remains to be formally tested, that the youths with conduct problems principally benefiting from current psychosocial interventions are those with heightened threat responsiveness and that treatment works by reducing amygdala responsiveness to threat.

Although it has been demonstrated that psychosocial interventions reduce the increased amygdala responsiveness to threat in patients with PTSD¹⁵⁸, there have been no findings that such interventions can increase a reduced amygdala responsiveness to distress cues, although this may be possible. There have been some reports that psychosocial interventions can reduce levels of callous–unemotional traits¹⁶⁰, particularly in adolescents from families with high parental warmth^{160,161}. Of course, in the absence of fMRI studies of treatment efficacy, it is also possible that these more successful interventions may alter only the behavioural manifestation of the psychopathic traits in specific social contexts rather than the pathophysiology underlying the psychopathic traits itself.

There is evidence that atypical antipsychotic drugs have some efficacy in the treatment of aggression in children^{162,163}. Certainly, their usage is common; it is estimated that in the USA, over 70% of youths with disruptive behaviour disorders are given antipsychotics¹⁶⁴. The atypical antipsychotic aripiprazole is a partial agonist at dopamine D2 and serotonin 1A receptors^{165,166}, and the antipsychotic risperidone has been shown to markedly increase extracellular levels of dopamine, serotonin, noradrenaline and acetylcholine in the rat medial PFC¹⁶⁷. Studies have shown that some of the dysfunctions seen in youths with psychopathic traits can be mimicked through manipulation of the seroton-ergic and dopaminergic systems. For example, serotonin depletion disrupts the recognition of fearful expressions and impairs performance on reinforcement-based decision-making tasks (passive avoidance learning and reversal learning)^{168–170} — tasks in which adolescents with psychopathic traits show impairment. The neuro-transmitter dopamine is important for reinforcement signalling^{56,171,172}, and dopamine depletion has been shown to disrupt performance on reinforcement-based decision-making tasks¹⁷³. Dopamine antagonists reduce the amygdala responsiveness to threat stimuli¹⁷⁴, and dopamine agonists increase the amygdala response to fearful expressions¹⁷⁵. Thus, neuroscience might provide a computational underpinning for the idea that the atypical antipsychotics are beneficial for adolescents with conduct disorder and psychopathic traits. However, it should be noted that atypical antipsychotics

have considerable side effects¹⁷⁶, including weight gain¹⁷⁷ and type 2 diabetes mellitus¹⁷⁸. As such, future studies should address whether these compounds do indeed normalize the patient's pathophysiology.

Conclusions and future directions

Psychopathic traits are characterized by core impairments in empathy, particularly in the processing of distress cues, and core impairments in decision making, specifically in prediction error signalling and the representation of reward outcomes and expected value. These impairments are associated with dysfunction in the amygdala, vmPFC and striatum, although other brain areas may also be involved (FIG. 2). These impairments, with some exceptions, are also seen in adults with psychopathic traits (BOX 4). Studies in animals are increasing our understanding of these computational impairments.

A molecular neuroscience-level understanding of this disorder is crucial for the development and refinement of treatments, but this is currently only at an early stage. Importantly, it is now possible to model aspects of the empathy and decision-making impairments in animals. For example, mice show observational learning from the emotional displays of other mice⁵⁴, and rats can perform a task that is very similar to the passive avoidance task used to study individuals with psychopathic traits^{179,180}. Such animal models allow us to target brain areas for molecular investigation that cognitive neuroscience studies of psychopathic traits have shown to be relevant to the disorder.

Perhaps the most important promise of neurobiological studies into psychopathic traits is that they may identify biomarkers that can provide differential diagnoses and predict long-term prognosis and treatment efficacy. Although differential diagnoses can be provided on the basis of an individual's overt behaviour and their self-report of impairment, they are prone to environmental influences on behaviour, inaccuracies in self-report and clinician biases. It can be argued that, at least in the future, diagnosis by identifying pathophysiology is more likely to be relevant for treatment decisions¹⁸¹. Currently, we only have putative fMRI and neurocognitive biomarkers of psychopathic traits^{8,76}. Studies will need to be conducted to determine whether they predict long-term prognosis and treatment efficacy. With respect to prognosis, some preliminary findings show that reduced amygdala volume, reduced aversive conditioning and lower error-related brain activity predict future offending^{74,182,183}. These will need to be confirmed. Currently, we have no data on whether the putative fMRI and neurocognitive biomarkers of psychopathic traits predict treatment response. Moreover, we have no data on whether current treatments alter the pathophysiology of psychopathic traits. But fMRI studies will allow us the possibility of determining whether current (and novel) treatments address the underlying pathophysiology rather than the immediate behavioural manifestation of this pathophysiology.

There has been rapid development in our understanding of the cognitive neuroscience of psychopathic traits over the past 5 years — the first fMRI studies into the neural correlates of psychopathic traits in youths only appeared in 2008 (REFS 8,9). The collection of data is accelerating and new avenues of research, such as modelling the functional impairments in animals and molecular neuroscience approaches, are becoming available. It is perhaps time

to believe that we will soon be able to more effectively help adolescents with psychopathic traits.

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Abbreviations

Observational fear	The phenomenon that an infant's avoidance responses to a previously novel object are modified by the mother's apparent emotional reaction to this object. Typically, infants avoid objects associated with maternal fear
Transgressions	Actions that violate norms
Passive avoidance learning	An experimental paradigm in which the individual learns to approach or passively avoid (by not responding to) objects that elicit either reward or punishment (for example, money gain or loss)
Operant extinction	An experimental paradigm in which the individual learns that responding to an object is rewarding but then, after a change of reinforcement contingency, should extinguish this response as responding comes to be associated with punishment
Reversal learning	An experimental paradigm in which the individual initially learns to make a response towards one of a paired set of stimuli to gain reward but then, after a change of reinforcement contingency, should reverse their behaviour towards the second object as the first object comes to be associated with punishment
Prediction error	The difference between the amount of reward or punishment received and the amount expected
Expected value	The expected reward or punishment following the commission of a specific response
Functional anisotropy	A parameter in diffusion tensor imaging, which images brain structures by measuring the diffusion properties of water molecules. It provides information about the microstructural integrity of white-matter tracts

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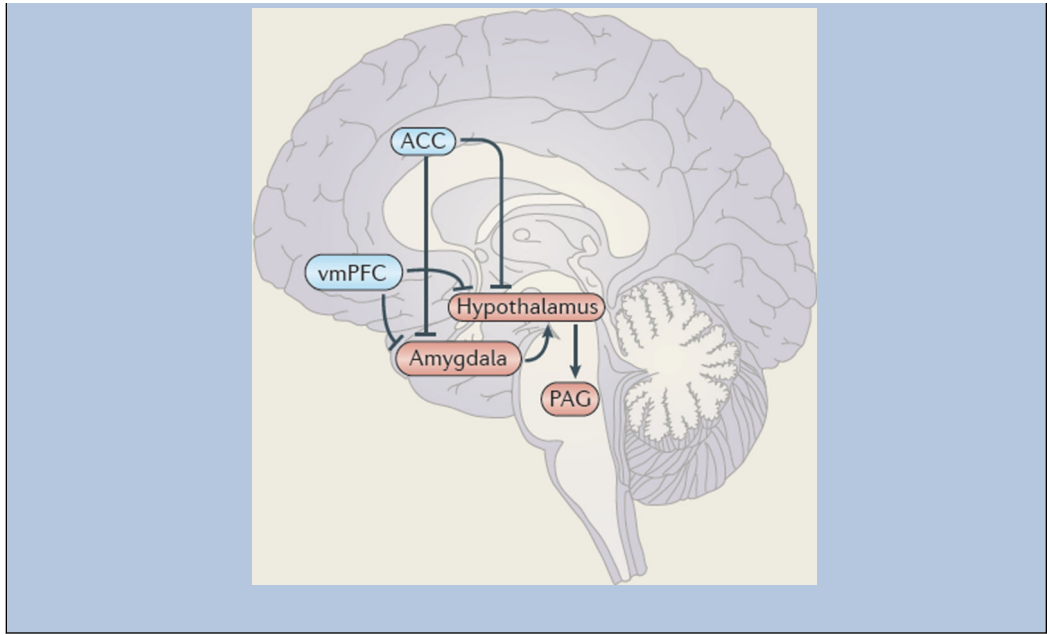
Box 1**Different forms of conduct disorder**

Patients receiving a diagnosis of conduct disorder do not all have the same pathophysiology. One set of neurodevelopmental impairments — decreased amygdala responsiveness to distress cues and decreased striatal and ventromedial prefrontal cortex (vmPFC) sensitivity to reinforcement signals that are critical for successful decision making (FIG. 1) — can lead to a diagnosis of conduct disorder associated with psychopathic traits. Another set of dysfunctions can also lead to a diagnosis of conduct disorder, as explained below.

Mammals demonstrate a graded and instinctual response to threat: distant threats induce freezing; as the threats draw closer, they induce flight; and, finally, reactive aggression is induced when they are very close and escape is impossible¹⁸⁴. Reactive aggression involves unplanned, enraged attacks on the object perceived to be the source of the threat or frustration. Animal studies have shown that reactive aggression is mediated by a circuit that runs from the medial amygdala, largely via the stria terminalis to the medial hypothalamus, and from there to the dorsal half of the periaqueductal grey (PAG)^{185–188}.

This circuitry is assumed to mediate reactive aggression in humans as well¹⁸⁹ (see the figure). Certainly, several recent functional MRI studies have identified these regions to be involved in defensive reactions to threat in humans^{190–192}. This circuitry is assumed to be regulated by frontal cortical regions, particularly the vmPFC and, potentially, regions of the anterior cingulate cortex (ACC).

If the basic threat circuit (amygdala–hypothalamus–PAG) is overly responsive, either because of prior priming or inadequate regulation, the individual is more likely to respond to a threat with reactive aggression than with freezing or flight⁵³. In youths with conduct problems and low callous–unemotional traits, this circuit is overly responsive, as evidenced by, for example, increased amygdala responses to fearful expressions⁴⁹. Moreover, they are more likely to display higher levels of threat-based and frustration-based reactive aggression¹⁹³. Such individuals probably represent many of the 40% with conduct disorder who also meet criteria for a mood or anxiety disorder¹⁹⁴. Notably, a high rating for psychopathic traits (which characterizes the other form of conduct disorder) is typically associated with a decreased risk for anxiety and mood disorder symptoms, particularly when the relationship between anxiety on the one hand, and antisocial and impulsive behaviour on the other hand is accounted for^{195–197}. This inverse relationship between psychopathic traits and mood and anxiety disorders is unsurprising, as increased amygdala responsiveness is also commonly associated with mood and anxiety disorders¹⁹⁸. By contrast, psychopathic traits are associated with decreased amygdala responsiveness^{8,10,30,48–50,83}.



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Box 2**Care-based moral judgements**

The deficits in emotional empathy and reinforcement-based decision making in adolescents with psychopathic traits affect social cognition in these individuals, particularly the formation of appropriate care-based moral judgements (that is, judgements about transgressions that result in harm to another individual (for example, one person hitting another), known as care-based transgressions). It has been argued that emotion has an important role in care-based moral judgments^{199–202}. Specifically, care-based judgments rely on the amygdala associating the aversive emotional response to the victim's distress with the representation of the action that caused this distress and on the ventromedial prefrontal cortex (vmPFC) representing the value of the transgression⁵³. Adults with psychopathic traits show reduced amygdala and vmPFC activity in response to care-based transgressions and a weaker correlation between their amygdala response and their rating of the severity of care-based transgressions compared with control participants^{203,204}. Similarly, youths with psychopathic traits show reduced amygdala activity and reduced amygdala–vmPFC functional connectivity when making moral judgements⁸³. There is also behavioural evidence that youths (and adults) with psychopathic traits show impaired care-based moral reasoning^{69,199}. In addition, a recent study showed that adolescents with psychopathic traits give less to charities when such giving comes at a personal cost²⁰⁵.

Perhaps the most interesting finding regarding the altered moral reasoning in individuals with psychopathic traits is that it is selective for care-based transgressions. Indeed, their moral judgement of conventional transgressions (which concern social normative behaviour and are heavily reinforced by the anger of hierarchy figures (for example, not talking during class)) and disgust-based transgressions (transgressions that may elicit disgust reactions from observers — often against forms of sexual activity)^{69,199,206–208} is normal^{69,199,209,210}. In addition, adults with psychopathic traits (adolescents have not yet been tested) judge care-based transgressions less seriously than control individuals, whereas there are no differences in how they judge the severity of conventional and disgust-based transgressions^{209–211}.

It has been argued that the ability to respond to emotional reactions of others is critically important in socialization (including in judging social transgressions). As partially independent emotional learning systems are thought to allow the learning of valence information provided by different emotional expressions^{25,53}, a selective impairment in processing care-based transgressions may be due to impairment in a particular emotional learning system. Specifically, distress cues (for example, from people subjected to care-based transgressions) are processed by the amygdala; the inferior frontal cortex is involved in processing angry expressions (which occur during conventional transgressions; for a meta-analytic review of the expression literature, see REF. 212); and the insula is important for processing disgust expressions (which occur during disgust-based transgressions)²⁰⁰. Thus, the selective impairment in recognizing distress cues but not disgusted or angry expressions in individuals with psychopathic traits (for meta-analytic reviews of the literature, see REFS 27,28) is in agreement with the finding that

such individuals show impaired processing of care-based transgressions but normal processing of conventional and disgust-based transgressions^{69,199,209,210}.

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Box 3**The development of psychopathic traits**

There are considerable genetic influences on the development of the systems considered here (the amygdala, caudate and ventromedial prefrontal cortex (vmPFC)) and their interconnections^{213–215}. It is assumed that the genetic contribution to psychopathic traits results in a disruption of this development, but this remains to be empirically confirmed. Environmental variables (such as enrichment, diet and parental deprivation) also influence the development of these structures^{216–218} and some (for example, alcohol abuse) may induce modulation of gene expression²¹⁹. As such, they may have a role in the development of psychopathic traits, although this also remains to be empirically confirmed (there is some evidence that parental warmth may have an impact^{160,161}).

Dysfunction in these structures will give rise to reduced anxiety and to decision-making deficits. However, it is argued that, by itself, this dysfunction will not give rise to core features of psychopathic traits, such as decreased guilt and conscience and increased antisocial behaviour and instrumental aggression⁵³. Rather, these are thought to be developmental consequences of the dysfunction in these brain structures that disrupt successful socialization. Socialization requires the individual to develop an association between the aversive reinforcement of the victim's distress cues and the representation of the antisocial actions that induced this distress⁵³. Future representation of this action will thus engender the negative expected value (the 'badness') of this action. The negative expected value will guide the individual away from the antisocial action and make the individual feel bad should they commit the action (guilt will occur if the individual represents their own causal role in the antisocial behaviour). In line with this, increased levels of the temperamental trait 'fearfulness' are associated with increased conscience development and guilt^{220,221}. The argument is not that socialization occurs through fear but rather that fearfulness is a measure for the integrity of the amygdala. The amygdala is critical for the development of the associations that are the basis of socialization.

It is worth considering the influence of adolescence on psychopathic traits. Mid-adolescence is associated with a period of enhanced responsiveness to threat and reward^{222–225}, as well as gradual maturation of systems implicated in top-down attention and response control (that is, the dorsomedial, superior and lateral frontal cortices)^{226,227}. The increased reward sensitivity in mid-adolescence may increase antisocial behaviour in youths with psychopathic traits. Such an individual may be more likely to seek means — including antisocial means if these have been learnt — to achieve their goals and may remain relatively insensitive to the negative actions of their behaviour for others. The mid-adolescence increase in functional integrity of frontal systems engaged in top-down control has not yet been associated with any effect on the severity of psychopathic traits.

Finally, the developmental impact of substance abuse on the pathophysiology of psychopathic traits should be considered, as psychopathic traits are a risk factor for substance abuse²²⁸, and substance abuse usually commences in mid-adolescence. Importantly, substance use has been associated with atrophy in, among others, the

amygdala and vmPFC^{229–231} and thus is likely to further disrupt the functional integrity of neural systems that are already dysfunctional in youths with psychopathic traits.

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Box 4**Comparing youths and adults with psychopathic traits**

Cognitive neuroscience studies have shown similarities and differences between youths and adults with psychopathic traits (see the table; following recent methodological criticisms about some work on adults with psychopathic traits²³², this comparison includes only clinical populations that are matched for IQ or for whom IQ differences are statistically considered).

Youths with psychopathic traits and adults with psychopathic traits are notably similar in terms of their functional impairments. Both show reduced psychophysiological responsiveness to the distress of others and impaired recognition of emotional (particularly fearful and sad) expressions, extinction, reversal learning and care-based moral judgement. Adults with psychopathic traits also show impairment on aversive conditioning tasks, but such studies have not yet been conducted in younger individuals.

A comparison of structural MRI (sMRI) studies shows that amygdala volume is reduced in both youths and adults with psychopathic traits. Findings regarding the integrity of the uncinate fasciculus in these groups are inconsistent. In addition, adults with psychopathic traits seem to have reduced structural integrity of the ventromedial prefrontal cortex (vmPFC), but there are no consistent findings in younger patients.

Functional MRI (fMRI) studies have shown reduced functional connectivity between the amygdala and vmPFC in both youths and adults with psychopathic traits. Findings of reduced amygdala responses to emotional provocation in adults with psychopathic traits are similar to reduced amygdala responses to fearful expressions found in youths with psychopathic traits. But studies that specifically examined the response to fearful expressions in adults with psychopathic traits have typically not shown reduced amygdala responses^{233–235} (but see REF. 236). However, it is difficult to draw conclusions from these studies, as only the study that reported group differences actually observed an amygdala response to fearful expressions in the comparison individuals²³⁶.

fMRI studies have shown that youths with psychopathic traits have reduced responsiveness to reward within the vmPFC^{64,76}. However, reward responsiveness has not been investigated in adults with psychopathic traits. Of the two fMRI studies in adults with psychopathic traits that have reported vmPFC dysfunction, one study reported reduced vmPFC differential responsiveness to moral versus non-moral images²⁰⁴, whereas the second study reported increased vmPFC activity in individuals identifying another person's emotional responsiveness²³⁷. Given the differences in task between these two studies and the lack of specific investigations of reward responsiveness, it is not currently possible to conclude whether there is consistency between youths and adults with respect to vmPFC functioning.

In short, cognitive neuroscience findings in youths and adult with psychopathic traits are relatively similar — this is perhaps not surprising and indicates that the underlying pathophysiology is similar. It is likely that future studies will identify differences. For example, long-term drug abuse, which is increased in individuals with psychopathic

traits²²⁸, may have progressively deleterious effects on brain structure and function, and may exacerbate pre-existing pathophysiology and cause additional dysfunctions.

Data	Youths	Adults
<i>Functional impairments (neurocognitive testing)</i>		
Psychophysiological responsiveness to the distress of others	Reduced (as measured by skin conductance responses) ³⁹	Reduced (as measured by skin conductance responses) ^{42,238,239}
Expression recognition	Impaired ^{27,28}	Impaired ^{27,28}
Aversive conditioning	Unclear	Impaired ⁷¹
Extinction	Impaired ⁶⁵	Impaired ²⁴⁰
Reversal learning	Impaired ⁶⁸	Impaired ²⁴¹
Care-based moral judgement	Impaired ⁶⁹	Impaired ^{199,242,243}
<i>sMRI findings</i>		
Amygdala	Reduced ⁹³⁻⁹⁷	Reduced ^{121,244}
vmPFC	Inconsistent findings	Reduced ^{121,245,246}
Uncinate fasciculus	Inconsistent findings	Reduced connectivity ¹⁰³⁻¹⁰⁵
<i>fMRI findings</i>		
Amygdala-vmPFC functional connectivity	Reduced ^{8,83,106}	Reduced ¹⁰⁴
Amygdala responsiveness to emotional cues	Reduced ^{8,10,30,48,49}	Reduced ^{203,204,247}
vmPFC responsiveness	Reduced to reward ^{64,76}	Inconsistent findings

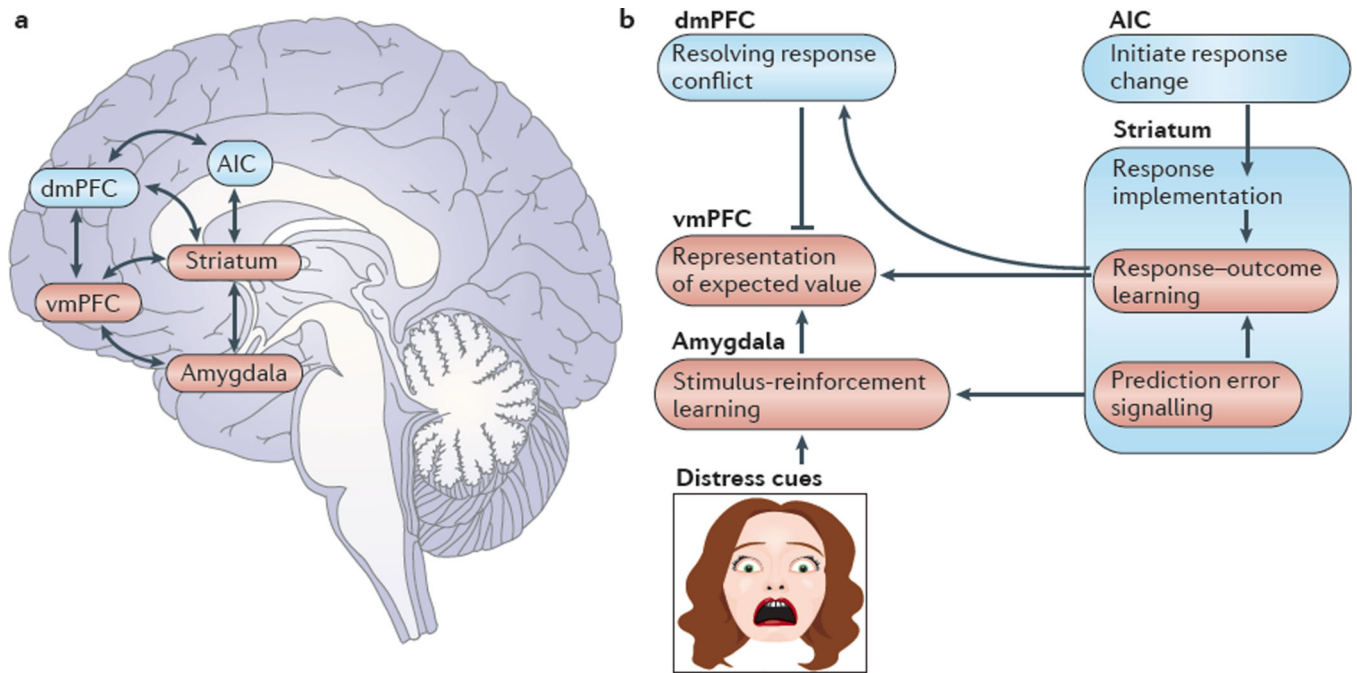


Figure 1. Core regions implicated in, and functions disrupted by, psychopathic traits

a | Core regions implicated in psychopathic traits: the amygdala, the caudate (which is part of the striatum) and the ventromedial prefrontal cortex (vmPFC). In addition to these core regions, the anterior insular cortex (AIC) and the dorsomedial PFC (dmPFC) may also be implicated. **b** | Functional impairments associated with psychopathic traits. In individuals with psychopathic traits, impaired processing of distress cues results in impaired learning about actions that harm others (stimulus-reinforcement learning), which involves the amygdala. In addition, impaired prediction error signalling in these individuals, which involves the striatum, causes impairments in both stimulus-reinforcement and response–outcome learning. As a result, the expected value of objects, cues and responses are poorly learnt and represented (in the vmPFC), and decision making is impaired. Response conflict resolution (which involves the dmPFC), initiation of response change (which involves the AIC) and response implementation (caudate) — functions implicated in guiding an individual away from suboptimal behavioural choices — are thought to be generally intact in individuals with psychopathic traits. These regions are also recruited to guide an individual away from suboptimal behavioural choices based on expected value information, that is, because the response about to be made is associated with punishment. Individuals with psychopathic traits show reduced recruitment of these areas on the basis of expected value information.

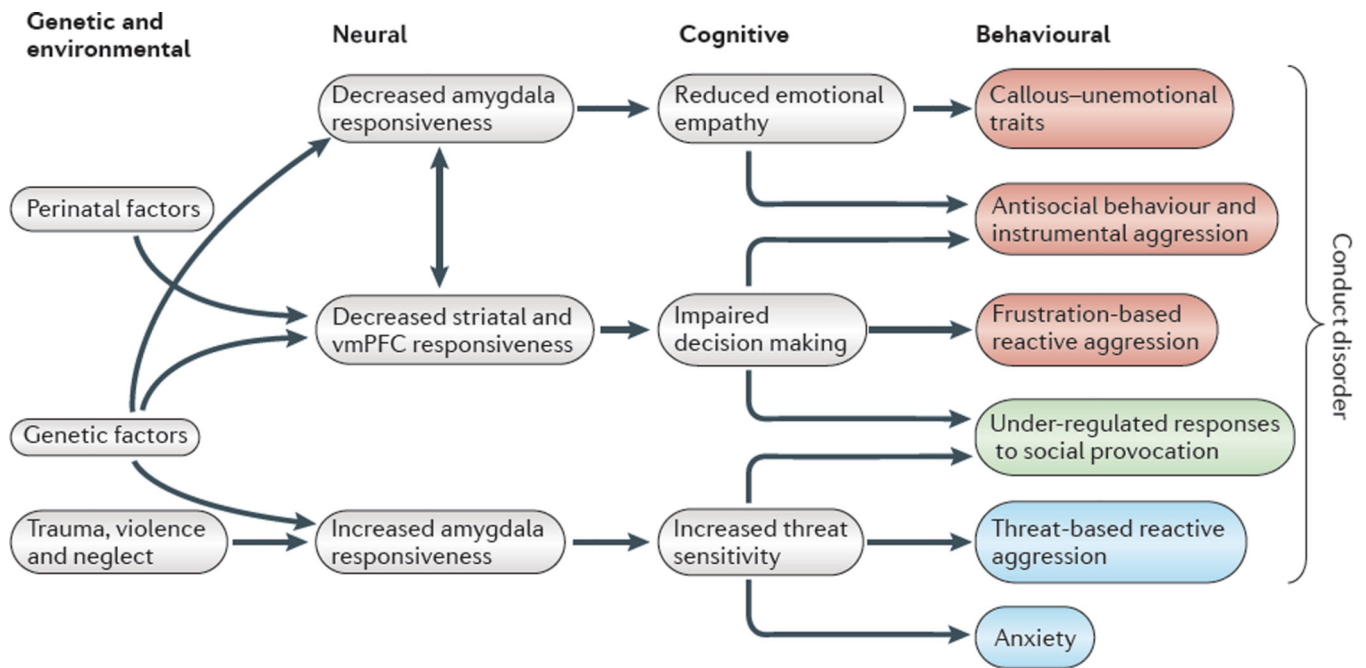


Figure 2. A framework for understanding conduct disorder

This model shows the aetiological (genetic and environmental), neural, cognitive and behavioural aspects of conduct disorder. Genetic factors reduce amygdala activation, specifically in response to distress cues, and consequently reduce emotional empathy. Genetic factors may also influence striatal and ventromedial prefrontal cortex (vmPFC) responsiveness to prediction error and expected value information and thereby lead to impaired decision making, but this has yet to be empirically demonstrated. Owing to the extensive interconnections between the amygdala, striatum and vmPFC, early dysfunction in one area is likely to be associated with dysfunction in the others. Perinatal factors, such as maternal substance abuse during pregnancy, can affect the functional integrity of these regions. All of these factors may lead to similar dysfunction at the cognitive level and may result in callous–unemotional traits and in increased antisocial behaviour and instrumental aggression. Impairments in decision making increase the risk that these individuals fail to achieve their goals, become frustrated and demonstrate frustration-based reactive aggression. Specific genetic polymorphisms as well as exposure to trauma, violence and neglect can result in increased amygdala responsiveness, specifically to threat cues. Such increased responsiveness increases threat sensitivity and the likelihood that a threat triggers reactive aggression (as opposed to freezing or escape behaviour). Increased amygdala responsiveness is also associated with an increased risk for anxiety disorders. Thus, patients meeting criteria for conduct disorder can have callous–unemotional traits or high levels of anxiety: callous–unemotional traits are associated with reduced amygdala responses to threat, whereas anxiety is associated with increased amygdala responses to threat. This suggests that there are at least two forms of conduct disorder. The first is referred to here as ‘conduct disorder with psychopathic traits’ and includes behaviours marked in red. The second is known as ‘conduct disorder associated with anxiety and emotional lability’ and

includes the behaviours marked in blue (also see BOX 1). Both forms are likely to show under-regulated responses to social provocation (marked in green).

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