Neural mechanisms of aggression

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Abstract | Unchecked aggression and violence exact a significant toll on human societies. Aggression is an umbrella term for behaviours that are intended to inflict harm. These behaviours evolved as adaptations to deal with competition, but when expressed out of context, they can have destructive consequences. Uncontrolled aggression has several components, such as impaired recognition of social cues and enhanced impulsivity. Molecular approaches to the study of aggression have revealed biological signals that mediate the components of aggressive behaviour. These signals may provide targets for therapeutic intervention for individuals with extreme aggressive outbursts. This Review summarizes the complex interactions between genes, biological signals, neural circuits and the environment that influence the development and expression of aggressive behaviour.

Aggression is a complex social behaviour that evolved in the context of defending or obtaining resources[1]. Although some features of aggression are species-specific, there are broad similarities across species (BOX 1). Neurobiological experiments show that many of the same neurochemical and anatomical systems are activated during aggressive behaviour in humans and non-human animals, even though the specific behavioural outputs can differ greatly. This Review takes a bottom-up approach to assess how genes and the environment contribute to the functioning of neural mechanisms of aggression. We discuss new data on molecules that are associated with aggression and that have been revealed by pharmacological and gene-targeting techniques, primarily in rodents. We will also examine the neuroanatomical organization of aggression in several contexts. This Review will show that the complex nature of aggressive behaviour necessitates a comprehensive approach that considers both genetic and environmental factors.

Aggressive behaviour

Traditionally, aggression has been defined as overt behaviour that has the intention of inflicting physical damage on another individual[2], and the potential for aggressive behaviour exists whenever the interests of two or more individuals conflict. Although aggression can yield competitive advantages, it is time-consuming and can be dangerous. When it is exaggerated, persistent or expressed out of context, it can be considered pathological. Psychiatrists and other care providers are particularly vulnerable to the serious consequences of violent outbursts in their patients, and an overarching goal of research into aggression is to develop interventions that can reduce maladaptive or pathological aggressive behaviour. In many cases, these interventions must be specifically tailored because of the patients' vulnerability, especially in the case of aggressive children or geriatric patients. To understand the mechanisms that underlie aggression, we need more precision in reporting the antecedents and consequences of different types of aggression[3]. From an ethological perspective, aggression is used for obtaining or defending food or mates from competitors; from a psychiatric perspective, it is thought to be motivated by hypothetical constructs such as anger, irritation, frustration, fear and, in some cases, pleasure[4].

Two subtypes of aggression have been identified in humans: the controlled–instrumental subtype and the reactive–impulsive subtype[5]. Reactive aggression is considered to be more impulsive (it is usually associated with anger), whereas instrumental aggression is considered to be more purposeful and goal-oriented. The instigation of a fist fight with a stranger who accidentally bumped into you on the street would be an example of reactive aggression. This subtype of aggression can result in sudden, heightened, enduring or inappropriate aggressive responses, and probably accounts for most societal problems that are associated with aggression. However, higher profile incidents (mass killings, genocides or assassinations) may be rooted in more instrumental mechanisms of aggression. The controlled–instrumental subtype of aggression is thought to be regulated by higher cortical systems and less dependent on the hypothalamic and limbic systems that are known to mediate impulsive aggression. Attacking your neighbours to intimidate them into not talking to the police would be an example of instrumental aggression.

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Box 1 | Limits to animal models

Studies of non-human animals have shed light on the behavioural, neurobiological and molecular mechanisms of aggression. Relating these mechanisms to the human condition is difficult because aggressive behaviours are so diverse. Fighting in non-human animals consists of combinations of biting, wrestling and chasing, whereas aggression in humans can take both physical and verbal forms. Although this diversity limits direct comparisons, it is possible to look for similarities between species in components of aggression. Darwin observed that both humans and other animals respond to social challenges with increased heart rate and respiration[109], well before the functional consequences of these responses were understood. Darwin also noted that some facial expressions, such as protrusion of the lower lip (pouting), are expressed by children and non-human primates in similar social contexts[109]. These observations show that differences in affective states between humans and other species are more quantitative than qualitative. It is also clear that much of the neural circuitry involved in the regulation of aggression in non-human animals is also functional in humans[110], albeit in different contexts. Rather than comparing overt aggressive behaviours between species, a more effective strategy might be to focus analyses on the motivational systems that influence the decision to engage in aggression.

Another problem with animal models is that most aggression tests only assess the quantitative aspects of the aggressive encounters. Pathologically aggressive individuals do not fight more furiously in a situation when anyone would fight; they fight in situations in which virtually nobody else would fight[111]. Better aggression tests are needed in the laboratory to assess the quality as well as the quantity of aggression, and to map it onto human aggressive psychopathologies.

A final difficulty is that studies on non-human animals are conducted under controlled settings, effectively eliminating the variation in environmental factors that might have crucial effects on behaviour. Many studies using animal models have shown that castration reduces male aggression[112], but a direct link between testosterone and aggression in humans has been difficult to establish[113]. One area in which there appears to be more consistency is how hormone levels change in response to social cues. Increased testosterone in response to a confrontation, also known as the challenge effect, has been observed in many vertebrates[114]. In humans, an increase in testosterone can be induced by a range of social challenges[105,115]. We are only beginning to understand the functional consequences of these dynamic changes in steroids. The example of the challenge effect shows that approaches that integrate social, hormonal and neurobiological perspectives will be more effective for understanding the neurobiological mechanisms of human aggressive behaviour.

Mental disorders such as intermittent explosive disorder, post-traumatic stress disorder, irritable aggression and depression-linked aggression are associated with increased autonomic arousal, which can contribute to sudden and uncontrolled reactive aggression. In contrast, individuals who are diagnosed with conduct disorder or antisocial personality disorder show unusually low autonomic responsiveness[6], which can contribute to increased instrumental aggression by blunting the typical emotional responses[7]. Thus, exaggerated aggressive responses can be observed in both high- and low-arousal states, with different biochemical and anatomical systems contributing to behaviour in each context. These examples show the importance of considering the broader behavioural context when attempting to study the mechanistic bases of aggression. The development of animal models that mimic specific aggressive disorders could lead to additional insights into the mechanisms that underlie aggression.

Intervention

A major goal of aggression research from a biomedical perspective is to develop interventions that can control inappropriate aggression among individuals. The results of this endeavour have been mixed. The development of neuroleptic drugs more than 50 years ago dramatically changed how clinicians manage violence in people suffering from mental disorders. Indeed, the effectiveness of chlorpromazine and haloperidol in reducing violent behaviour is used as a standard for evaluating new compounds[8]. First-generation neuroleptics worked primarily by sedation and had negative side effects such as tardive dyskinesia. The newer drugs are less sedating, but still produce similar negative side effects during chronic treatment[9]. Most current drug treatments of aggression involve the so-called 'second generation' or 'atypical' antipsychotics. For instance, risperidone is effective for some patients, such as children with autism spectrum disorder, who display maladaptive aggression. Risperidone, which antagonizes serotonin (5-hydroxytryptamine; 5-HT) type 2 (5-HT_2) and dopamine type 2 (D_2) receptors, has an increased risk of body-mass gain and other metabolic side effects. Other atypical antipsychotics have not been evaluated in the treatment of aggression in controlled double-blind studies. However, additional third-line drug-treatment options exist, including divalproex (an antiepileptic) and lithium. As noted, psychiatric illnesses, substance abuse and dementia can all produce a chronic problem with aggression; despite pharmacological advances, there is still much room for improvement. Treatment of aggressive animals has even fewer management options. Although there are behavioural modification treatments for dogs that bite other dogs, the primary treatment for dogs that bite humans is isolation or death.

Neural circuits of aggression

The characterization of the neural circuits that control aggression is difficult because these circuits also regulate other social behaviours. Indeed, it has been suggested that aggressive behaviours are emergent properties of a social behaviour network[10] that includes the medial preoptic area (MPOA), lateral septum (LAS), anterior hypothalamus (AHA), ventromedial hypothalamus (VMH), periaqueductal grey (PAG), medial amygdala (MEA) and bed nucleus of the stria terminalis (BNST) (FIG. 1).

Rodents. In rodents, inputs from the olfactory bulb[11] are sent to the MEA and then relayed to the BNST, MPOA, LAS, AHA, VMH and PAG[12] (FIG. 1a). This pathway is not linear, as there are many interconnections among these nuclei. It has also been proposed that different subnuclei are more active in different social contexts. For example, the posteroventral MEA and dorsomedial VMH are thought to be more important for regulating aggression in defensive contexts, whereas the posterodorsal MEA is thought to be more important in offensive contexts[13]. The components of this network have been identified mainly through lesion studies and investigations of immediate early gene expression. In general, lesions of the LAS, BNST, AHA and MEA reduce aggression between males[14]. Lesions of the orbitofrontal cortex (OFC) increase aggression in male rats[15], indicating that higher cortical networks have inhibitory effects on the social behaviour network. Electrical stimulation of

Intermittent explosive disorder
A disorder characterized by repeated episodes of aggressive, violent behaviour that is grossly out of proportion to the situation; thought to affect as many as 7.3% of adults in the United States.

Neuroleptic drug
An antipsychotic drug that is used to treat various psychiatric disorders, including schizophrenia. Although these drugs have stabilizing effects on mood, a major drawback is that they have potent sedative effects.

Tardive dyskinesia
A disorder characterized by twitching of the face and tongue and involuntary motor movements of the trunk and limbs.

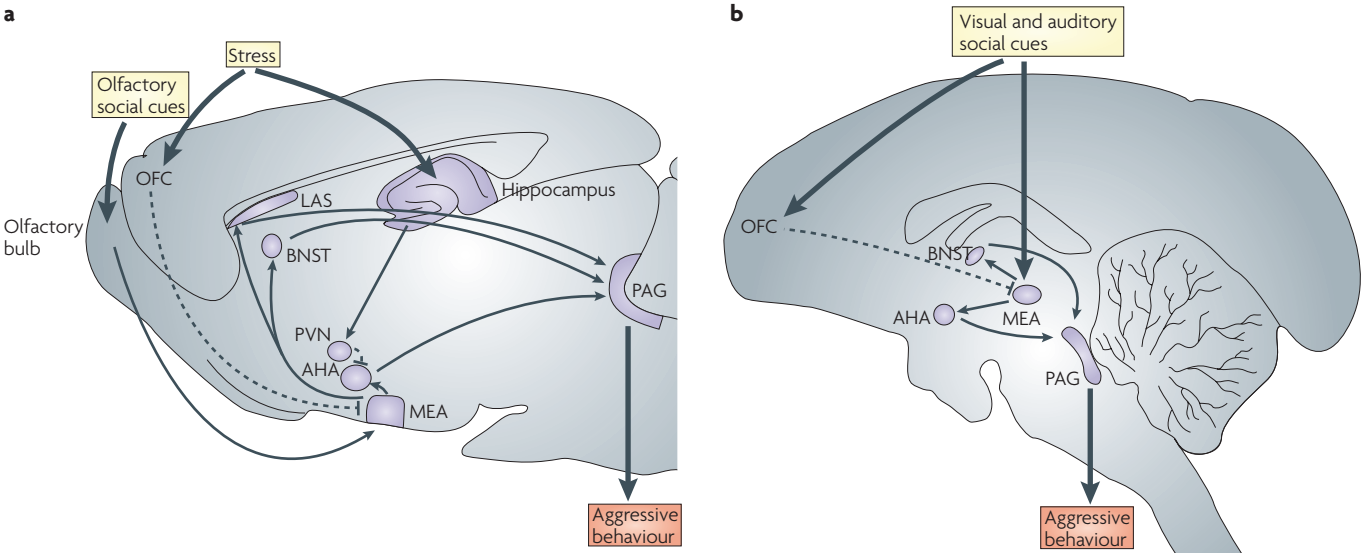

Figure 1 | **Neuroanatomical pathways of aggression in rodents and non-human primates. a** | In rodents, information from the olfactory bulb is processed by the medial amygdala (MEA) and sent to the lateral septum (LAS), bed nucleus of the stria terminalis (BNST) and anterior hypothalamic area (AHA). These brain areas are thought to prompt the periaquaductal grey (PAG) into promoting species-specific aggressive behaviours. Stress can inhibit aggression via inhibitory inputs from the orbital frontal cortex (OFC), the hippocampus and the paraventricular nucleus (PVN). **b** | In non-human primates, aggression is typically evoked by vocal or visual signals. Activation of the MEA is thought to result in activation of the BNST and AHA, which in turn activate the PAG. In general, the OFC appears to be important for the interpretation of social cues, and inhibitory inputs from the OFC might inhibit aggression by reducing responsiveness in the amygdala. Thick arrows represent inputs and outputs to and from the brain; thin arrows represent connections within the brain; dotted lines represent inhibitory connections.

the AHA increases male aggression[16], whereas microinjection of a vasopressin-receptor antagonist into the AHA decreases male aggression[17]. Investigation of immediate early gene expression has identified several nuclei that are activated by fighting. For example, immunostaining for the immediate early gene product FOS is increased in the LAS, BNST, AHA and MEA in several contexts, including male–male aggression[12,18], female–female aggression[19] and maternal aggression[20].

Non-human primates. As in rodents, the hypothalamus seems to have a key role in regulating aggression in non-human primates (FIG. 1b). Electrical stimulation of the VMH increases vocal threats and piloerection (an aggressive display) in male marmosets (*Callithrix jacchus*)[21]. Similarly, lesions of the AHA and preoptic area (POA) reduce vocal threats towards an intruder in male *C. jacchus*[22]. In rhesus monkeys (*Macaca mulatta*), electrical stimulation of the AHA, BNST or POA increases the frequency of aggressive vocalizations[23], and increases aggression towards subordinate males[24].

Recent studies have focused on the amygdala and OFC. Lesions of the amygdala either increase[25] or decrease[26] inter-male aggression in rhesus monkeys. One explanation for these conflicting results is that the study that reported increased aggression reintroduced lesioned monkeys into groups (potentially a more threatening and fear-inducing situation), whereas the study that found decreased aggression tested monkeys in groups of two[26], which might be less threatening. Lesions of the OFC are generally associated with reduced affiliative behaviour such as grooming or close contact[25], whereas their effects on aggressive behaviour depend on context. For example, OFC lesions produce increased aggression in dominant, but not subordinate, males[25]. In a different study, OFC lesions in dominant animals led to an initial increase in aggression that disappeared after several months[27]. In general, it appears that the OFC is important for the interpretation of social cues, and that it contributes to appropriate behavioural responses in complex social situations.

Humans. Brain-lesion and brain imaging studies suggest that neural circuitries that mediate reactive aggression in humans have some homologies with the networks that control aggression in non-human animals[28,29]. In humans, many studies have reported a link between brain damage to the frontal cortex and increased aggressive behaviour[30]. These findings are consistent with reports that individuals who rank highly on measures of reactive aggression show lower-than-average baseline activity in the frontal cortex[31,32].

The frontal cortex provides inhibitory inputs to circuits in the hypothalamus and amygdala that might promote aggression[29], although the role of these brain areas is less well established in humans than in other animals. In one study, individuals that had been diagnosed with intermittent explosive disorder showed increased activation in the amygdala in response to angry faces when compared with control participants, and amygdala activation across both groups was positively correlated with scores on the Lifetime History of Aggression (LHA) scale[33]. Brain injury rarely causes selective damage

Immediate early gene
A gene that is expressed rapidly and transiently in response to various cellular stimuli. Several of these genes (for example, *Fos* and *Egr1*) are used by neuroscientists as indirect markers of neuronal activity because they are expressed when neurons fire action potentials.

Vasopressin
A neuropeptide that is present, among other regions, in the anterior hypothalamus and is known to affect aggression.

Piloerection
The erection of hair on the skin, used as a threatening display by many animals.

to the hypothalamus or amygdala; however, during a grim period in the mid-twentieth century, electrolytic lesions of these brain regions were used to treat what was deemed 'excessive aggression'[34]. Although lesions of the hypothalamus and amygdala were reported to inhibit aggression, these conclusions are limited because the measurement of behaviour was usually crude, and the studies failed to account for the complexities of human behaviour[35]. Additionally, electrolytic lesions damage areas penetrated by the electrode as well as the target nuclei, and damage to the hypothalamus and amygdala affects general arousal[36], not just aggression. Although an experimental approach is desirable to infer cause and effect, a more integrative and ethical approach is required in studies of human aggression.

Several recent studies have taken an integrative approach to elucidating the neurobiological circuits that influence aggression in humans. Previous work showed that individuals who rated highly for impulsive aggression had reduced activation of the prefrontal cortex (PFC), and selective serotonin-reuptake inhibitors (SSRIs) reduced their ratings of aggression[37]. On the basis of these findings, the effect of SSRIs on PFC activity was examined in patients who had been diagnosed with borderline personality disorder. People diagnosed with this disorder tend to score highly on measures of impulsive aggression. Twelve weeks of SSRI treatment increased baseline activation in the PFC, and PFC activation was negatively correlated with ratings of aggression[38]. In addition, positron emission tomography (PET) imaging studies using a selective 5-HT receptor type 1A (5-HT_{1A}) antagonist showed that scores on the LHA scale were negatively correlated with 5-HT_{1A} binding in the amygdala and PFC[39]. Furthermore, intranasal administration of the neuropeptide hormone oxytocin in humans reduced amygdala activity in response to fear-inducing pictures (for example, of sharks and snakes)[40]. Studies in animals indicate that oxytocin can reduce aggression[41–43] and that oxytocin receptors are abundant in the amygdala[44]. Thus, oxytocin might reduce human aggressive responses in some contexts, although this hypothesis needs to be tested directly. Targeted neurochemical manipulations, a realistic social context and sophisticated refinements in the assessment of aggression will allow investigators to ethically test in humans hypotheses that have been developed using animal models.

Biological signals and aggression

The evaluation of biological signalling molecules has provided additional clues about the neural circuits that are involved in complex social behaviours. The activation of specific neurotransmitter receptors evokes cascades of signal-transduction molecules through distinct, but highly interacting, second-messenger systems and multiple effectors (Supplementary information S1 (table)). Below, we review some of the important signalling molecules that have been linked to aggression.

5-HT. Numerous studies have demonstrated that 5-HT can affect aggressive behaviours. Generally, low 5-HT levels are associated with higher levels of impulsivity and aggressiveness[45], and manipulations that lower 5-HT signalling increase impulsivity and aggression[46]. Conversely, increasing 5-HT activity with 5-HT precursors, 5-HT-reuptake inhibitors or 5-HT_{1A}- and 5-HT_{1B}-receptor agonists can reduce aggressive behaviour in rodents[46,47]. Both gene-targeting and pharmacological approaches have been used to investigate the role of 5-HT receptors in aggression (reviewed in REFS 47,48). The 5-HT_{1B} receptor is expressed in many brain regions, including those involved in aggression, such as the PAG, hippocampus, LAS and raphe nuclei. This receptor acts either presynaptically, to inhibit the release of 5-HT, or as a heteroreceptor[49]. Activation of these 5-HT_{1B} receptors inhibits aggressive behaviour despite decreasing serotonergic tone; presumably the behavioural effects of 5-HT_{1B}-receptor activation reflect modulation of other neurotransmitter systems. Male mice that lack functional expression of the gene that encodes 5-HT_{1B} receptors (*Htr1b*$^{-/-}$ mice) are more aggressive than wild-type mice[50], presumably because the lack of these heteroreceptors removes the 'brakes' on aggressive behaviour. But given the low levels of aggression in the parental strain (129Sv), the 'enhanced' aggression in these knockout mice was low relative to other strains such as 129/B6 (REF. 49). More recent studies have implicated the 5-HT_{1B} receptor in the regulation of impulsiveness, rather than aggression *per se*[49]. Treatment with the 5-HT_{1B}-receptor agonist eltoprazine (a mixed 5-HT_{1A}- and 5-HT_{1B}-receptor agonist, and one of the so–called 'serenics') significantly reduces aggressive behaviour in both wild-type and *Htr1b*$^{-/-}$ mice, presumably by affecting non-5-HT_{1B} receptors in the knockout strain[51]. Thus, although 5-HT_{1B} receptors have an important role in the regulation of aggression, probably through their modulatory effects on impulsivity, additional 5-HT-receptor subtypes might also contribute to the control of aggressive behaviour.

Specifically, activation of 5-HT_{1A} receptors (by eltoprazine and other 5-HT_{1A}-receptor agonists) reduces aggressive behaviour. These results are consistent with the observation that mice that exhibit high levels of aggression, although still within the normal range, have increased availability of postsynaptic 5-HT_{1A} receptors in limbic and cortical regions[52]. Although both 5-HT_{1A} and 5-HT_{1B} receptors control 5-HT tone, they probably contribute differently, in specific brain areas, to the inhibitory postsynaptic effects of 5-HT on aggression. Changes in regional brain 5-HT synaptic availability in both *Htr1a*$^{-/-}$ and *Htr1b*$^{-/-}$ mice are not correlated with levels of aggression[53]. For example, although *Htr1b*$^{-/-}$ mice show increased aggression and 5-HT_{1B}-receptor agonists suppress aggression, treatment with 5-HT_{1B}-receptor antagonists does not enhance aggression. Mice that lack the 5-HT transporter (5-HTT) show reduced aggression and locomotor activity, an effect that is probably mediated by dysregulation of the 5-HT_{1A} and 5-HT_{1B} receptors[54].

Consistent with several psychopharmacological studies of rodents, PET scans of human volunteers treated with radio-tagged WAY-100635 (an antagonist for 5-HT_{1A} receptors) revealed a negative correlation between LHA scores and 5-HT_{1A}-binding potential[55]. This result supports the idea that 5-HT_{1A} has an inhibitory influence on aggression.

Lifetime History of Aggression (LHA) scale
An interview-based scale that is used by mental health workers to assess general aggressive tendencies in humans. Interviews can be supplemented with other sources such as clinical records.

Selective serotonin-reuptake inhibitors
A class of antidepressants that inhibit the reuptake of serotonin (5-HT) by neural cells, thereby increasing the amount of 5-HT in the synapse.

Borderline personality disorder
A disorder that is characterized by instability in moods, interpersonal relationships, self-image and behaviour; thought to affect approximately 2% of adults.

Heteroreceptor
A receptor that modulates the synthesis and/or release of neurotransmitters other than its own ligand.

Importantly, aggression evoked by electrical stimulation of the hypothalamus of rats is not affected by 5-HT_{1A}-receptor agonists, but it is reduced in a dose-dependent manner by treatment with 5-HT_{1B}-receptor agonists[49]. The distinction between a functional aggressive state (for example, normal territorial defence) and violent pathological outbursts is important[3,56]. A series of studies in which several 5-HT-receptor agonists and antagonists were administered while 5-HT levels were assessed by microdialysis showed that 5-HT levels increased sharply, albeit briefly, during both typical and pathological aggressive bouts in rats[56]. However, in pathological aggression, the increase in 5-HT levels is preceded by a strongly inhibited basal serotonergic tone, which could therefore serve as a trait that is characteristic of pathological aggression.

The continued discovery of 5-HT-receptor subtypes indicates that further study will be needed to clarify the specific roles of the various receptors and their interactions in aggression. Indeed, it would be instructive to examine aggressive behaviour systematically in knockout mice that lack other 5-HT-receptor subtypes, as well as in tissue-specific 5-HT-receptor knockout mice, to discriminate between pre- and postsynaptic effects of 5-HT signalling on aggression. The development of additional specific 5-HT-receptor agonists and antagonists will also aid our understanding of the mechanisms that underlie aggression. Furthermore, increased temporal precision is necessary to assess how moment-to-moment changes in 5-HT levels correspond with changes in aggressive behaviour. In general, it appears that 5-HT sets the tension of the 'trigger' for aggression, mainly by limiting impulsivity.

Dopamine. Aggressive behaviour seems to require that the mesocorticolimbic dopaminergic neurons be intact[3]. These neurons also contribute to other motivated behaviours such as reproductive and maternal behaviours, as well as food and drug intake. The D_2-receptor antagonist haloperidol has been used effectively for decades to treat aggressive patients, especially those who are psychotic[57]. Indeed, although many atypical antipsychotics act on different dopamine receptors, those that can ameliorate aggression that is associated with increased arousal share the ability to antagonize the D_2 receptor. The effect of D_2-receptor activation on aggression might be mediated by changes in arousal or stress responses[3]. Indeed, haloperidol has sedating and locomotor-impairing effects, which make it and other D_2-receptor antagonists unattractive for long-term treatment of aggression.

The role of dopamine in aggression has been further elucidated in animal experiments. Animals can be conditioned to increase dopamine secretion in anticipation of aggressive interactions[58], which suggests a connection with instrumental aggression. Antagonists of both the D_1 and D_2 receptors reduce aggression in male mice[57]. Two isoforms of the D_2 receptor have been identified, termed D_2L (the long form) and D_2S (the short form), and male mice that lack the D_2L receptor showed reduced aggression compared with wild-type mice[59]. Disruption of the dopamine transporter (DAT) reduces both the temporal and spatial resolution of dopaminergic neurotransmission and leads to increased extracellular dopamine concentrations, as well as reduced expression of D_1 and D_2 receptors in the striatum. DAT knockout mice showed increased reactivity and aggression[60]. The combined decrease in D_1 and D_2 receptors and increased aggression in DAT knockout mice is somewhat surprising given that antagonists of these receptors decrease aggression. It suggests that dopamine has different effects on aggression during development and in adults.

Thus, although dopamine is necessary for the appropriate expression of aggressive behaviour, the precise role of dopamine and its receptors in modulating aggression remains unspecified. The blocking of D_2 receptors might serve to reduce arousal or stress responses[3], which would reduce aggression that is associated with increased arousal. Indeed, drugs such as the D_2 antagonist risperidone are effective at reducing these types of aggression in humans.

GABA. Pharmacological manipulations that increase GABAergic activity in the septal forebrain increase aggression in rodents[61], and levels of GABA and glutamic acid decarboxylase (GAD), the enzyme that catalyses its production, are low in the brains of mice and rats that have recently engaged in aggressive responses[62].

Allosteric modulators of $GABA_A$ receptors, such as benzodiazepines, barbiturates and endogenous allopregnanolone influence aggression levels in rodents, with an inverted U-shaped dose–response curve; moderate doses evoke aggression, whereas low or high doses reduce aggressive behaviour[3]. The facilitative effects of alcohol on aggression are well known, and also occur through allosteric modulation of $GABA_A$ receptors[3]: alcohol increases the duration and frequency of opening of chloride ion channels and thereby enhances GABA-mediated chloride flux[61].

GABA-receptor agonists reduce aggression in many people, presumably by reducing arousal. The paradoxical observations that benzodiazepine treatment sometimes provokes violent behaviour in some patients led to preclinical dose–response studies, which revealed that both low and high doses of several benzodiazepines, including diazepam, diazepoxide and midzaolam, were associated with elevated aggressive behaviours in a small subset of patients. Individual differences in aggressive responses to alcohol or benzodiazepines probably reflect specific $GABA_A$-receptor subunit compositions (that is, α-, β- or γ-receptors)[3], which are likely to be determined by a combination of experience and genetic factors. Currently, it is not possible to predict which individuals will show paradoxical aggression with standard benzodiazepine treatment.

Noradrenaline. Antagonistic encounters are generally perceived as stressful and arousing, and elevated levels of noradrenaline, both centrally and peripherally, are characteristic of arousing situations[63]. Although no consistent relationship between noradrenaline and aggression has been found, pharmacological manipulations of noradrenaline levels or specific noradrenergic receptors indicate that noradrenaline signalling facilitates aggression[61]. The α- and β-adrenergic-receptor subtypes seem to contribute differently to aggressive behaviours. For

Glutamic acid decarboxylase
An enzyme that produces GABA (γ-aminobutyric acid) from l-glutamic acid in an irreversible reaction.

example, propanolol, which blocks postsynaptic β-receptors, reduces aggressive behaviour both clinically and in laboratory animals[61]. The contribution of α_2–receptors to aggression is more complicated, because agonists and antagonists evoke the same behavioural response — low doses increase aggression and high doses decrease it. These results might reflect the shifting dynamics of activation of presynaptic and postsynaptic α_2-receptors[64]. Drugs that decrease adrenergic responses, such as α_2 agonists and β-blockers, are used to treat children who show hyperarousal-induced aggression. Finally, the role of noradrenaline, in aggression was confirmed in dopamine β-hydroxylase knockout mice. These mice cannot produce noradrenaline, and have reduced aggression and impaired social memory, but normal anxiety responses[65].

Nitric oxide. Nitric oxide can function as a neurotransmitter[66]. Mice that lack neuronal nitric oxide synthase (nNOS), which transforms arginine into citrulline, have no nitric oxide in the CNS. *Nos1*$^{-/-}$ mice exhibit persistent fighting and sexual behaviour despite obvious signals of surrender or disinterest, respectively, by their test partners[67]. Castration sharply reduces aggression in *Nos1*$^{-/-}$ mice, whereas testosterone replacement restores it to pre-castration levels[68]. These results indicate that testosterone is necessary, but not sufficient, to elevate aggression in *Nos1*$^{-/-}$ mice. Individually housed wild-type male mice treated with a nNOS inhibitor are more aggressive than vehicle-treated mice, but this effect is absent when mice are pair-housed[69].

Mice that lack nNOS show significantly reduced 5-HT metabolism in several brain regions, including the cortex, hypothalamus, midbrain and cerebellum[46]. The concentration of 5-HT, but not that of its metabolite 5-HIAA (5-hydroxyindole acetic acid), is elevated in most brain regions that were studied in *Nos1*$^{-/-}$ mice. The disturbed neurochemical profile appears to be specific to the 5-HT system, as levels of noradrenaline, dopamine and their metabolites were generally unaffected. The normal concentrations of noradrenaline and dopamine indicate that alterations in monoamine oxidase (MAO) activity probably do not account for the 5-HT abnormalities in *Nos1*$^{-/-}$ mice[46], although MAO has been implicated in aggression (see below). Further work is necessary to understand the relationship between 5-HT and nitric oxide and how this relationship mediates aggression, but it is possible that nitric oxide normally acts as a brake on aggression in the presence of low 5-HT.

Monoamine oxidase A (MAOA). The metabolic enzyme MAOA affects aggression by altering neurotransmitter levels. MAOA catalyses the oxidative deamination of 5-HT, noradrenaline and dopamine with high affinity[70], and it is predominantly found in catecholaminergic neurons in the brain. MAOA deficiency, which is caused by a point mutation in the *MAOA* gene, has been correlated with impulsive aggression in several males from a Dutch family[71] (see below). Deletion of the *MAOA* gene in mice also leads to high levels of offensive aggression, despite elevated concentrations of 5-HT[72]. Chronic MAOA deficiency is associated with upregulation of adenosine A2A receptors[73] and abnormalities in the expression of 5-HT-receptor subtypes[70]. Chronic forebrain-specific restoration of MAOA expression in transgenic *MAOA* knockout mice normalizes 5-HT, noradrenaline and dopamine levels and eliminates the aggressive phenotype[74]. It is unclear whether the elevated aggression in the knockout mice reflects the elevated 5-HT or noradrenaline levels.

The mutation that causes impulsive aggression in a Dutch family produces an early stop codon in the gene for MAOA, which is located on the X chromosome. The mutation therefore renders affected males completely devoid of MAOA activity[71]. This mutation is relatively rare, and is not likely to account for much of the variation in human aggression and violence. However, there is wide variability in MAOA activity among the normal population. For example, a repeat length polymorphism (containing a variable number of tandem repeats) that lies upstream of exon 1 in the MAOA regulatory region contains four common alleles that have three to five repeats of a 30-base pair (bp) sequence[75]. *In vitro* experiments indicate that these allelic differences in humans could result in two- to tenfold differences in transcriptional activity in the *MAOA* gene[75]. In these studies, the cell lines expressing human alleles 2 and 3 (which have 3.5 or 4 copies of the 30-bp repeat, respectively) had *MAOA* gene expression at significantly higher levels than cell lines expressing alleles 1 and 4 (which have 3 or 5 copies of the 30-bp repeat, respectively)[75]. When this polymorphism was assessed in a community sample of men, those with alleles 2 or 3 (the high-transcription variants) showed reduced serotonergic responsivity and scored higher on a composite measure of aggressiveness and impulsivity than men with either of the other two alleles[76]. Furthermore, the high-activity MAOA allele 3 was also more common among boys identified by parents and teachers as being persistently aggressive[77]. Thus, both the complete absence of MAOA activity (in humans and mice) and increased MAOA activity within the physiological range (in humans) are associated with increased aggressive behaviour. These findings suggest that MAOA hypo- or hyperactivity can contribute to exaggerated aggression.

Steroid hormones. Several classes of steroid hormone might influence aggression (Supplementary information S1 (table)), but androgens and oestrogens have been studied in the most detail. Castration, which greatly decreases levels of circulating androgens, reduces male aggression in many species, although recent studies have documented exceptions[78,79]. Androgens have both organizational and activational effects on aggression: in addition to organizing the brain into a male-like pattern, androgen receptors promote the development of fighting behaviour through play[80]. In the post-pubertal period, testosterone (or oestrogenic metabolites) stimulates neural circuits that were organized perinatally, presumably by making aggression-inducing stimuli more salient.

Among rodents, the effects of testosterone on aggression are variable and may depend on the animal's genetic background[81]. For example, testosterone increases aggression in C57BL/6J mice, whereas the conversion

of testosterone to oestradiol by the aromatase enzyme is necessary to increase aggression in the CF-1 strain[81]. These steroids seem to promote aggressiveness at the level of the LAS, amygdala and dorsal raphe nucleus[81]. Consistent with the well-documented effects of castration and androgen replacement on male aggression, male mice exhibiting a spontaneous mutation that results in an inactive androgen receptor are not aggressive[82]. Although there is strong evidence for a causal link between testosterone and aggression in non-human animals, results from human studies are mixed. A positive relationship between testosterone and aggression emerges more consistently when testosterone is measured in response to competitive interactions (as opposed to responses on a questionnaire), either directly or vicariously[83].

Oestrogen signalling also influences aggressive behaviour. Male mice with targeted disruption of the gene for the α-isoform of the oestrogen receptor (ERα) show reduced aggression in several testing situations[84,85]. Furthermore, aggression in mice is positively correlated with the number of ERα-positive cells in the LAS, BNST and AHA, but not the MPOA[79] (FIG. 2). Conversely, mice that lack the β-isoform of the oestrogen receptor exhibit normal or increased aggression, depending on their social experience[86,87] or age[88]. Because oestrogens are essential for normal sexual differentiation of the mammalian CNS during development[86], studies of adult behaviour in ERα-knockout mice are complicated by the inability to dissociate genetic from ontogenetic causes of behaviour.

Genetic contributions to aggression. Male aggression was among the first behaviours to be examined across inbred strains of mice[89]. These early studies revealed that strain differences in behaviour could be modified by the environment. Mice of the least aggressive strain became more aggressive when they won fights, whereas social subjugation (defeat) reduced aggression in mice of a less aggressive strain[90]. Since these early investigations, many studies have reported a strong genetic contribution to murine aggression. Mice have been particularly useful in dissecting the contribution of genes to aggression because of the widely available genetic tools for these animals. However, strain differences have complicated the interpretation of knockout studies[47].

For example, a spontaneous mouse mutation named 'fierce' (*frc*) lacks the gene for nuclear receptor NR2E1 (also known as TLX, the mouse homologue of *Drosophila melanogaster* Tailless). The *frc* mutation results in an extremely aggressive phenotype in both males and females when bred into a C57BL/6J background, but the effect is less pronounced in a B6129F1 background[91]. The pathologically aggressive phenotype can be ameliorated by insertion of the human gene *NR2E1* (REF. 92). Owing to the extensive characterization of mice carrying the *frc* mutation, these mice provide a useful model to study how genetics and the environment interact to influence aggression. Currently, neither the neurochemical systems nor the neuroanatomical substrates for the NR2E1 protein have been studied, but the behaviour of *frc* mice is reminiscent of the unrelenting reactive subtype of human aggression.

Gene–environment interactions. Laboratory studies of aggression typically measure behaviour under a single set of environmental conditions. However, mechanisms of aggressive behaviour have evolved in fluctuating physical and social environments. Recent data indicate that the effects of several neurochemical pathways on aggression depend on experience. Thus, different behavioural phenotypes emerge in different environments (FIG. 3).

As mentioned, deficiencies in MAOA activity are associated with increased aggression in animal models, although in humans this relationship is less clear. The effects of the repeat length polymorphism described above appear to interact with the environment to affect behaviour. Caspi and colleagues[93] reported that the effect of child abuse on behaviour was significantly stronger if the child carried alleles associated with low MAOA activity. Abused children with low MAOA activity had increased antisocial behaviour, greater prevalence of conduct disorder and a higher likelihood of being convicted for violent offences than abused children with high MAOA activity (FIG. 3a). In children who were not abused, the polymorphism had no effect on these behavioural measures. This gene–environment interaction has been examined in several studies, and a meta-analysis indicated that, on average, children with genotypes for low MAOA activity have elevated rates of antisocial behaviour when exposed to parental maltreatment[94]. Although further study is needed, these results indicate that certain genetic backgrounds might confer resistance to adverse environmental conditions, which could partially explain why many abused children do not show increased antisocial behaviour.

The effects of gene–environment interactions can also be seen in 5-HT-regulated behaviours such as depression[95]. There is some evidence that environmental factors interact with variability in the 5-HTT gene to influence aggression. The short allele of the 5-HTT gene is associated with reduced expression of 5-HTT in the brain, inefficient reuptake of 5-HT from the synapse[96] and exaggerated responses to stress[97,98]. The interaction between stress and 5-HTT genotype was examined in men and women who were instructed to administer shocks to a confederate as punishment for incorrect responses in a memory task (no shocks were actually delivered)[99]. Half of the participants were subjected to a physical stressor, an unpredictable air blast to the throat, whereas the other half were not. Men, but not women, who were homozygous for the short allele of the 5-HTT gene were more likely to administer shocks in the stressful condition, whereas there were no genotypic differences in the control condition. This interaction could be mediated by differences in threat perception, as individuals carrying the short allele have increased activation in the amygdala in response to fear-inducing pictures[100].

A different form of gene–environment interaction has been identified in *Peromyscus polionotus* (beach mouse). As with hamsters, day length influences aggression levels, so that *P. polionotus* are more aggressive when exposed to short days than when exposed to long days[101]. Hormone-manipulation studies showed that the ERα agonist PPT (propylpyrazole-triol) and the ERβ agonist DPN

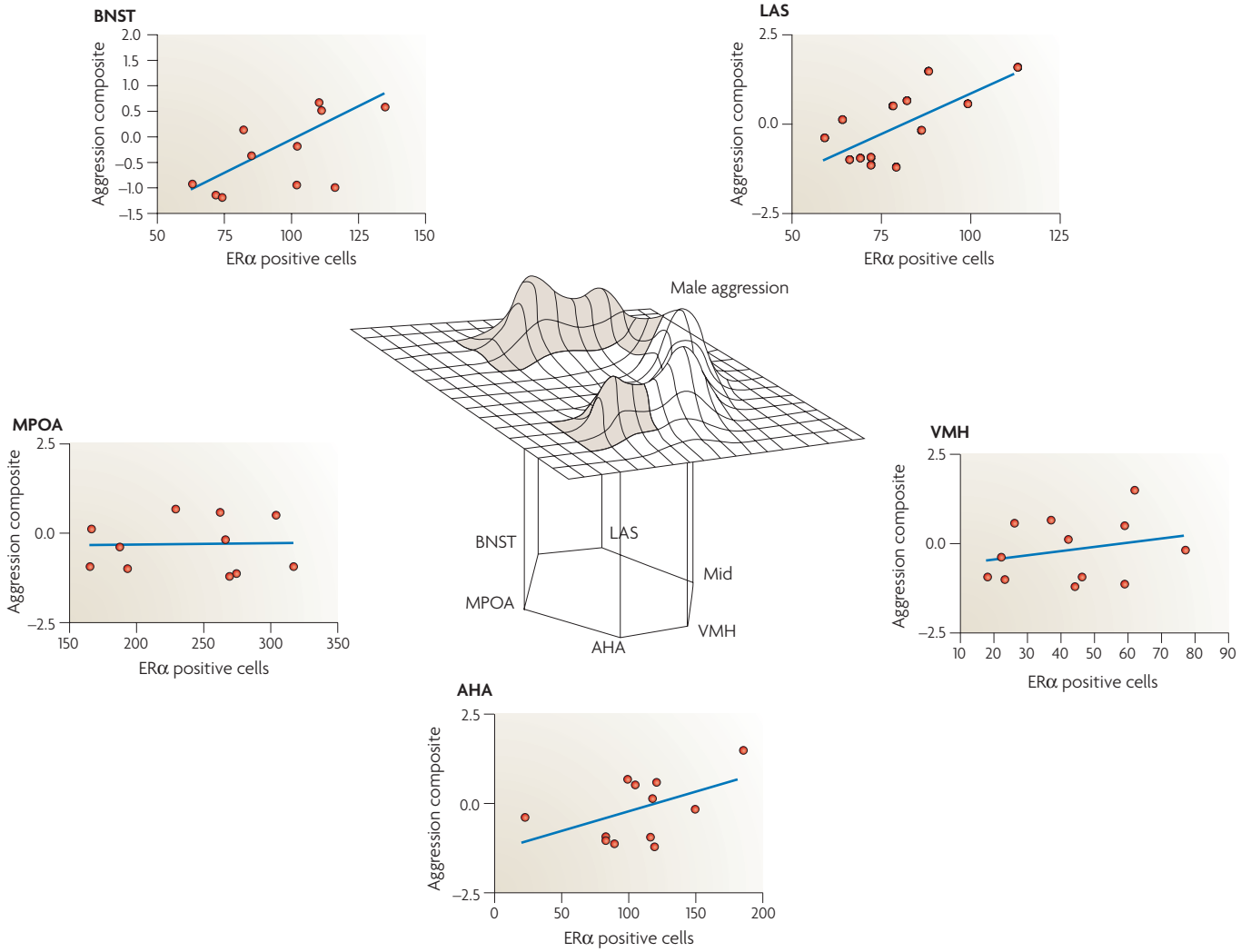

Figure 2 | **The relationships between oestrogen receptor-α (ERα) immunoreactive cells and aggression in the social behaviour network.** In CD-1 mice, aggressive behaviour is positively correlated with aggression in the lateral septum (LAS), bed nucleus of the stria terminalis (BNST) and anterior hypothalamus (AHA) (shaded areas of contour map), but not the ventromedial hypothalamus (VMH) or medial preoptic area (MPOA). ERα is not expressed in the midbrain (Mid). The contour map reflects the relative expression of FOS (an indirect marker of neuronal activity) following a male–male aggression test. Aggression composite scores were calculated by a principal component analysis of biting, boxing and attack latency. Positive scores indicate more aggressive mice and negative scores represent less aggressive mice. Graphs reproduced with permission from REF. 79 © (2006) Elsevier Sciences. Contour map modified with permission from REF. 10 © (1999) Blackwell Publishing.

(diarylpropionitrile) increased aggression in 'short-day' *P. polionotus* and decreased aggression in 'long-day' mice (FIG. 3b). These data suggested that photoperiod regulates processes that occur after oestrogens bind their cognate receptors. Steroids, including oestrogens, can affect physiological and behavioural processes via slow (hours to days) genomic or fast (seconds to minutes) non-genomic pathways[102]. In *P. polionotus*, oestradiol injections acted rapidly (within 15 minutes) to increase aggression in short- but not long-day mice[101]. This suggests that oestradiol increases aggression via non-genomic actions on short days but not on long days. Moreover, gene chip analyses indicated that oestrogen-dependent expression of genes containing oestrogen response elements in their promoters was decreased in the BNST of short-day mice compared with that of long-day mice[101]. These data suggest that the environment regulates the effects of steroid hormones on aggression in *P. polionotus* by determining the molecular pathways that are activated by steroid receptors.

Gene chip
A method for analysing the expression of numerous genes simultaneously.

Hormone response element
Sequences of DNA in promoter regions that are bound by hormone receptors. Binding of the receptor complex promotes transcription.

Integration

Neurochemical and neuroanatomical pathways of aggression have been investigated in various species, and it is apparent that some pathways are common to humans and non-human animals. Increasing serotonergic activity decreases reactive aggression in humans and also reduces aggression in a mouse resident–intruder test, probably by decreasing impulsivity. A more challenging task is determining how murine behaviour in a resident–intruder test relates to reactive or instrumental

Resident–intruder test
An aggression test in which an intruder is introduced into a resident's home cage. Residents are typically more aggressive because they are familiar with the environment and are defending their home territory.

aggression in humans. Aggression researchers have been struggling with this question, and a comprehensible answer has not yet emerged. This may be because there is no unambiguous answer.

In addition to 5-HT, dopamine also mediates aggression in a mouse resident–intruder aggression test. In humans, reactive aggression appears to be governed more by serotonergic pathways, whereas the motivated characteristics of instrumental aggression suggest a role for dopaminergic pathways. Given the enormous differences in biology and social structure, it is unlikely that mouse and human aggression can be classified into homologous categories. However, it is clear that many neurochemical systems (such as the serotonergic system) have coevolved in mice and humans to regulate species-specific aggressive behaviours. Thus, although aggressive behaviour is expressed in different contexts with different behavioural outputs in mice and humans, similar neurochemical and neuroanatomical pathways are activated.

Difficult questions remain to be answered. For example, to what extent does an impoverished background influence the development of these neurochemical and neuroanatomical pathways, and to what extent are they activated by observing aggression? Considerable debate ensues on the effects of violence in the media on aggression, and myriad confounding factors make it difficult to study these putative effects. Recent studies have demonstrated that aggression is increased in animals that observe conflicts among other individuals[103,104]. Generally overlooked by mental health researchers, these data show that vicarious experiences have important biological effects. Sports fans respond to watching their team win or lose with corresponding increases or decreases in testosterone levels[105]. Children playing violent video games show reduced activation of brain areas involved in affect, such as the amygdala and the anterior cingulate cortex[106]. Reduced brain activity in frontal areas has also been reported in children with high exposure to violent video games and television programmes[107]. Although it is not clear whether these experiences have long-term behavioural effects, it is clear that vicarious experiences have consistent short-term influences on brain activity. It is perhaps unsettling that these patterns resemble those identified in individuals with dysregulated aggression[31,32]. Biology-based approaches to examine the effects of observing violence on aggressive behaviour, if they are conducted in realistic social contexts (in addition to questionnaires and other pencil-and-paper approaches) have potential because they allow more precise measurements of the neural circuits that influence aggressive behaviours.

Another issue of concern to clinicians is how to treat uncontrolled aggression. This is a complicated issue because, although it is agreed that unchecked aggression has negative consequences, a certain amount of human aggression is probably necessary to succeed in life. Clinical trials have investigated many treatments aimed at reducing elevated aggression that is associated with mental disorders, but treatments that can ameliorate excessive aggression have unwanted side effects on processes such as arousal[108]. Although further advances in drug development may lead to additional improvements in the treatment of pathological aggression, the complexity of aggressive behaviour suggests that it might not be possible to control aggression. A more effective strategy for dealing with uncontrolled aggressive behaviour may lie in a combination of biological and behavioural approaches, especially for instrumental aggression.

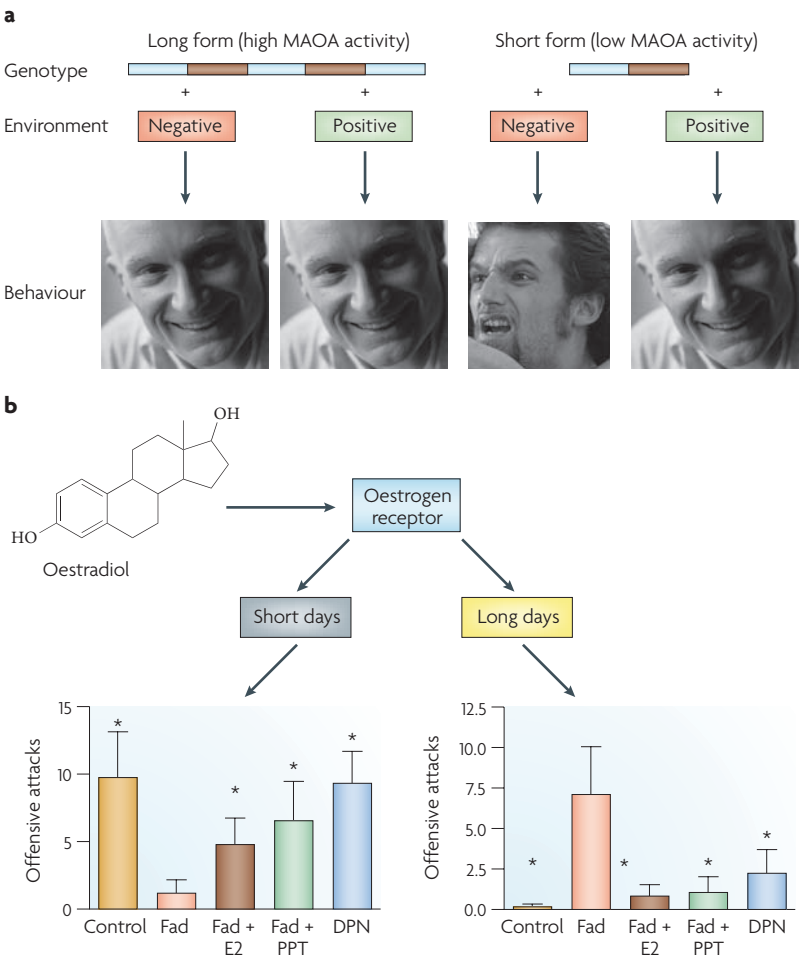

Figure 3 | **Gene–environment interactions in humans and mice. a** | The interaction between the monoamine oxidase A (MAOA) genotype and the rearing environment affects aggressive behaviour. Although they have not been replicated in every study, most data suggest that children carrying the short form of the MAOA promoter gene, which confers decreased MAOA activity, are more likely to develop conduct disorders and increased antisocial behaviour when exposed to abusive home environments. This environmental effect is less prevalent in individuals carrying the long form of the promoter. **b** | Photoperiod determines the directional effects of oestrogens on aggressive behaviour in beach mice (*Peromyscus polionotus*). *P. polionotus* are more aggressive when exposed to short days (shown in the left graph) than when exposed to long days (shown in the right graph). Treatment with the oestrogen synthesis inhibitor fadrozole (fad) decreases aggression if beach mice are tested in short days, but increases aggression if tested in long days. The effects of fad are reversed with co-treatment with oestradiol (E2). This does not appear to be mediated by differences in receptor expression, because the drugs PPT (propylpyrazole-triol, an oestrogen receptor (ER)-α agonist) and DPN (diarylpropionitrile, an ERβ agonist) both increase aggression on short days and decrease aggression on long days. Photoperiod apparently regulates the molecular actions of oestrogens, acting rapidly on short days (presumably non-genomically) and more slowly on long days (presumably genomically). Part **a** based on a paper by Caspi *et al.*[93]. Aggressive man image courtesy of BRANDX. Part **b** reproduced with permission from REF. 101 © (2007) National Academy of Sciences, USA.

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Competing interests statement
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