Stress and the social brain: behavioral and neurobiological mechanisms

Carmen Sandi[1] and Jozsef Haller[2]

(1) Brain Mind Institute, School of Life Sciences, Ecole Polytechnique Federale de Lausanne (EPFL), Switzerland.

(2) Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary.

Correspondence: carmen.sandi@epfl.ch

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

Abstract
Stress often affects our social lives. When undergoing high level or persistent stress, individuals frequently retract from social interactions and tend to be irritable and hostile. Predispositions to anti-social behaviors – including social detachment and violence – are also modulated by early-life adversity; however, the effects of early-life stress depend on the timing of exposure and genetic factors. Research in this emerging field in animals and humans has revealed some of the structural, functional and molecular changes in the brain. Findings in this field will have implications for the clinic and society.

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

Stress (here defined as the activation of the neurophysiological stress response) effectively helps organisms to cope with situations that challenge survival and promotes adaptation in response to threats to homeostasis[1-3]. However, sustained stress can have strong and long-lasting adverse effects on brain function and behavior[4, 5].

In the last two decades, there has been an explosion of research on how stress affects emotion and cognition. Although a social dimension of the stress response was recognized a century ago[6], much less is known about how stress can affect the brain circuits engaged in the processing of social information and articulation of social actions. However, the recent blooming of the social neuroscience field has stimulated an emerging interest in this field, and human epidemiological and clinical studies have revealed multiple examples of changes in social behaviors that seem to be linked to stress (BOX 1) — from income inequalities and economic crises (indirect indexes of stress) that uphold societal-level violence[7, 8] to severe stressors that induce marked dysfunctions in individuals' social functioning[9, 10].

Given the ethical constraints inherent in exposing individuals to high or recurrent stressful conditions, most studies in humans are observational or correlational. This has hindered the dissection of the specific impact of different types of stressors and time-windows of vulnerability in shaping social behaviors. Furthermore, different people are exposed to unique combinations of stressors during their lifetime and their effects are influenced by genetic, educational and social factors that are particularly relevant in humans and thus complicate human studies. For these reasons, translational animal models of stress and social behavior that are amenable to experimental control of potential confounds are important tools that may enable the dissection of neurobiological mechanisms at levels that are currently inaccessible to human studies.

This Review considers how various forms of stressors administered in different phases of the lifespan affect individuals' interest in and reactions towards conspecifics – including social motivation, social recognition and aggression – and analyzes the mechanisms that mediate such effects. Although there remain many gaps in our knowledge, the evidence accumulated so far has revealed surprisingly specific associations between the characteristics and concomitants of stress and its immediate and long-term consequences for brain function and social behaviors. These findings suggest that the development of novel intervention and treatment strategies for stress-related individual and societal problems will require a widening and deepening of our understanding in this important field of neuroscience.

Effects of stress on social behaviors

Most of the experimental work in this field employs rodents as animal models. Social behaviors in rodents are investigated using a variety of behavioral tests that assess different aspects of sociality (BOX 2). A consideration of the characteristic social behavioral profiles that result from different types of stress exposure (summarized below) reveals an interesting picture.

Stressors in adulthood

In rodents, acute stress – elicited, for example, by 'frustration' caused by omission of scheduled reinforcement or instigation by pre-exposure to a physically inaccessible intruder – typically leads to reduced social behaviors and increased aggression, including antisocial behaviours such as bite counts that exceed species-typical levels [11, 12]. This fits with the concept of acute stress as a 'flight or fight' response[6] and implies that brief acute stressors mobilize resources to cope with the situation.

Chronic stress (the stressor is recurrent or is sustained over several days) reduces social motivation and social interactions in a variety of sociability tests[13-15], particularly in highly anxious animals[16]. For example, chronic social defeat induces social avoidance and social fear towards unknown conspecifics[17], with the severity of these effects depending on the type and length of the defeat. However, although chronic stressors generally reduce sociability, social isolation stress actually enhances social interest[18], probably because long-term deprivation from social contacts

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

increases interest in social partners. Social interactions with an animal's kin are also affected by chronic stress, as indicated by a disruption of paternal behavior and pairmate interactions in the monogamous, biparental California mouse (*Peromyscus californicus*) male subjected to chronic variable stress[19].

Aggressiveness is increased by chronic physical stressors — including chronic unpredictable mild stress[20], restraint or immobilization[13-15, 21] — in mice and rats, as well as by social stressors such as social isolation[18, 22] in rodents and social and spatial restrictions in dogs[23]. Interestingly, chronic immobilization escalated both normative aggressive behavior (attacking small adversaries with a high chance of winning) and 'risky' aggression (attacking big adversaries, with a low chance of winning) in rats[21]. By contrast, chronic social stressors that involve fighting that leads to defeat and subordination have been shown to down-regulate aggressiveness in a variety of species. These effects frequently last for at least one month and are observed even when subjects are confronted in their homecage by smaller opponents[24-27]. Conversely, repeated victories – which are accompanied by reduced physiological stress responses but can be considered stressful because they involve recurrent exposure to social conflicts – may result in exacerbated and abnormal aggression [28, 29].

Stress during development

Stress models that cover a range of neurodevelopmental periods have been applied to investigate the long-term impact of stress on adult social behaviors (BOX 3). Social motivation (sociability) was disrupted in adulthood by prenatal[30]; neonatal[31, 32] and juvenile [33-35] exposure to stressors. By contrast, the execution of social behaviors in the social interaction test was affected differentially by stressors administered at different ages. Prenatal stress[30], neonatal stressors (maternal separation[36] and early deprivation[37]) and peripubertal exposure to physical stressors[35] inhibited social interactions in adulthood. Interestingly, early social deprivation also inhibited pair bonding in mandarin voles (Microtus mandarinus)[32]. Juvenile social stressors (post-weaning social isolation[38] and early subjugation[39]) either did not affect this aspect of social behavior or, in one study[40], increased adult social interactions.

The effects of early stressors on adult behavior in the resident–intruder test are even more variable. Here, prenatal stress reduced aggressiveness[41]. Maternal separation, by contrast, increased inter-male aggressiveness in rats (but not mice, although female mice showed increased maternal aggression[42]). Specifically, the latency of attack was reduced and/or the duration of offensive threats was increased, although bite counts remained unchanged[43]. Early deprivation increased all three components of aggression[32] and stressors administered to juveniles also enhanced aggressiveness in adulthood[35, 44-46].

Importantly, antisocial features of aggression were found to emerge mainly when animals were stressed at juvenile ages. All symptoms of 'antisociality' (see BOX 2) were observed in both the post-weaning social isolation and peripubertal non-social stress models[35, 47, 48]. However, only the subjects of the post-weaning social isolation model – but not the animals exposed to non-social peripubertal stressors – showed strong signs of behavioral agitation and defensiveness. The long-term consequences of early subjugation are different and include the expression of adult-type aggressiveness in juveniles, enhanced responses to provocation, and offensive ambiguity[45, 49, 50]. It is interesting to note that similar differences were found in studies that compared the long-term neural consequences of social and non-social stressors administered to juveniles[51]. Interestingly, antisocial features of aggression, particularly offensive ambiguity[52, 53], were also seen in the early social deprivation model.

These findings demonstrate that early life stressors decrease measures of social motivation, reduce the expression of social behaviors, increase aggressiveness, and promote the development of antisocial features, but the specific consequences depend on the timing and type of the early stressor(FIG. 1). Although these changes can be problematic for human individuals and societies, from an evolutionary perspective they could be interpreted as mechanisms through which early adversity prepares the organism to endure similar adversities later in life[54]. For example, enhanced

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

fighting readiness may confer adaptive advantage under subsequent social pressures, such as physical attacks or competition for scarce resources. Epigenetic programming may be a critical mechanism for mediating these long-term effects of stress on brain function and behavior[55].

Intergenerational effects

Animal studies have shown that the effects of stress on social behaviors in males can be transmitted to the next generation without direct contact between the stressed subject and his offspring, excluding the possibility that the transmission is a result of direct social learning. For example, a reduction in social exploration and reduced social memory was found in male mice submitted to stressors during early postnatal life, as well as in their offspring across two generations[31]. In rats, both the female and male F2 offspring of dams exposed to chronic stress during lactation displayed decreased social behavior as juveniles and adults[56]. Similarly, the offspring of peripubertally stressed male rats that had had no direct interactions with their father showed increased aggression[48]. Several mechanisms may drive these transgenerational effects, including changes in the females (such as altered maternal behavior[56] and/or physiological changes) that mated with the stressed male and epigenetic processes transmitted through the germline [57]. However, these possibilities require investigation.

The role of glucocorticoids

When a stress response is triggered, a rise in plasma glucocorticoid levels, resulting from the activation of the HPA axis, closely follows the initial activation of the sympathetic nervous system. The lipophilic nature of glucocorticoids enables their access to the brain, where they exert a broad range of molecular, structural and functional effects[58] through mineralocorticoid receptors (MR) and glucocorticoid receptors (GR; which mediate their effects through both genomic (slow) and non-genomic (rapid) mechanisms)[59, 60]. In addition to imediate effects of the activation of these receptors, glucocorticoids can also exert long lasting programming effects on brain function and behavior[58, 61-63].

Changes in glucocorticoid levels in stress models

Stressful experiences frequently alter the 'set-point' of the HPA axis, which can result in permanent changes (either increases or decreases (BOX 3)) in basal and/or stress-induced glucocorticoid levels. Alterations in the magnitude of stress-induced glucocorticoid responses can have both immediate effects in brain function through non-genomic mechanisms and long-term effects mediated by changes in gene transcription; however, the latter mechanism is predominantly involved when basal glucocorticoid levels are affected[64-69]. These changes in glucocorticoid levels seem to contribute to many of the changes in social behaviors induced by stressors. Three of the rodent developmental stress models resulting in antisocial aggression discussed above — early deprivation[64], early subjugation[39] and peripubertal stress[35] — are characterized by long-term decreases in HPA-axis activity (BOX 3). A fourth model — post-weaning social isolation — is characterized by normal basal HPA-axis activity, but enhanced autonomic and glucocorticoid responses to stress[65], which may drive the increased-stress induced aggression seen in adults in this model [11, 12].

Alterations in the glucocorticoid response to stress could result from molecular and cellular adaptations within different components of the HPA-axis as well as in the brain regions that regulate HPA-axis activity. For example, stress induces changes in the expression of GRs in the hippocampus, prefrontal cortex, and amygdala (all of which regulate HPA axis activity)[1, 2] and in the neural circuitry — including the preoptic area and other hypothalamic nuclei projecting to the periventricular nucleus — that regulates the activity of hypothalamic neurons expressing corticotropin releasing hormone (CRH)[3].

Effects of manipulating glucocorticoid levels.

Studies that have investigated the effect of exogenous glucocorticoid administration at different ages have provided support for the notion that glucocorticoids mediate, at least in part, the effects of

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

stress on social behavior. These treatments induced effects on social behaviors that were highly consistent with those seen in stress models. Corticosterone treatment in neonates[66] mimicked the diminished adult social exploration and increased submissiveness observed in maternally deprived mice[31, 32, 42]. Corticosterone treatment in juvenile rats[67] diminished social exploration as did exposure to peripuberty stress[35, 68-70] and acute glucocorticoid treatments in adulthood[71] increased aggressive behavior as did acute stress elicited by frustration[11, 12].

Other studies have mimicked the long-term effects of early stress exposure on HPA-axis function. For example, acute glucocorticoid treatments in adulthood that mimicked the HPA-axis alterations resulting from post-weaning social isolation decreased sociability and social behavior and increased aggression[69, 72]. In another example, mimicking the reduction in HPA axis activity in adulthood caused by early deprivation, early subjugation and non-social peripubertal stressors (through adrenalectomy with low-level glucocorticoid replacement)[72] led to decreased social behaviors and antisociality. This was abolished by repeated glucocorticoid treatments[73, 74] suggesting that the long-term suppression of HPA-axis function and the altered social behavior in these models are causally related. Therefore, both excesses and deficits in glucocorticoid production have detrimental effects on social behavior.

These findings indicate that glucocorticoid signaling at least partly mediates the behavioral effects of stress. Further support for this notion was provided by a study which showed that activation of GRs in dopamine receptor-expressing neurons in mesocorticolimbic and striatal circuits promoted social aversion induced by a subchronic social defeat procedure in mice[75]. Moreover, in humans, an interaction between genetic variation in the gene encoding FKBP5 (a cochaperone of heat shock protein 90 that affects the transcriptional capacity of GRs) and childhood trauma influences both lifetime history of aggressive behavior[76] and the glucocorticoid response to stress[77]. These findings suggest that individual differences in the neurodevelopmental trajectories leading to antisociality might be related to genetic variation in HPA-axis-related genes that affect the functioning of the stress systems during development and its consequent promotion of long-lasting epigenetic adaptations[76, 78].

Changes in social brain systems

The concept of the 'social brain' emerged in the context of brain imaging studies, and refers to brain areas that are activated in humans by social cognition tasks. It typically includes areas involved in social recognition (fusiform area, superior temporal gyrus and accessory olfactory bulb), context evaluation (amygdala, temporal and prefrontal cortices), social motivation (ventral tegmental area, nucleus accumbens and ventral pallidum) and execution of social behaviors (hypothalamus, and brainstem motor and autonomic pathways)[79]. Studies in animals have revealed a 'social brain network' that largely overlaps with the human social brain[80,81] (FIG. 2). In addition, a key role for the periaqueductal gray (PAG) in aggression in animals has been identified and recently confirmed in humans studies[82,83]. These findings substantiate the view that interactions between conspecifics are governed by homologous brain networks in mammals. Stress is a strong modulator of brain structure and function[5] and most of the brain areas that are particularly vulnerable to stress (such as the amygdala, prefrontal cortex, hippocampus and mesolimbic system) exhibit functional and/or structural alterations in individuals with abnormal social behaviors[84, 85].

Inappropriate social behavior that is not due to a brain lesion is usually assumed to be due to altered brain development (which might be caused by stress), impaired social learning (which could also be due to stress) and an inability of the brain to maintain normal structure and function under pressure (including stress)[86-89]. Although brain development, social learning and remodeling of brain circuits are not independent of one another (for example, neonatal stress may alter brain function and endocrine stress responses such that social learning becomes difficult), the relative contribution of these three factors to the effects of stress on social behavior changes across the lifespan. Prenatal and very early postnatal stress particularly impinge on brain development, whereas stress during

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

childhood and adolescence can also affect social learning. Chronic stressors in adulthood probably exert their effects by remodeling brain circuits that are involved in social behavior, whereas acute stressors seem to drive the adaptive mechanisms of the organism. Different families of cell adhesion molecules play roles in brain development, plasticity and cognition, and recent work has implicated several cell adhesion families in stress-induced alterations in social behaviors (BOX 4).

Structural changes

Developmental trajectories in the brain are strongly altered by prenatal stress or high pregnancy anxiety, which leads to grey matter volume reductions in several brain areas (prefrontal cortex (PFC), hippocampus and hypothalamus) in humans[90, 91] and rodents[92-94]. Rodent studies suggest an important role for glucocorticoid-induced apoptosis in some of these effects[95]. Structural changes in the same brain areas were observed when chronic stressors were administered to adult rodents[96-98]. Stress at other developmental stages also causes structural alterations. For instance, neonatal stress affected dendritic organization and synaptic plasticity in the PFC in rats[99-101]. Post-weaning social isolation specifically reduced the volume of posterodorsal component of the medial amygdala and of the right medial PFC in rats[102, 103]. However, neural plasticity markers, neuron numbers and basal metabolic activities were not altered in the limbic brain after early social subjugation in rats and hamsters[104-106], suggesting that structural changes are minimal following this stressor. Interestingly, early deprivation increased neuron numbers and decreased apoptosis throughout the hypothalamus[107], whereas it had mixed effects in different hippocampal fields [108]. Taking into consideration the important role of the hypothalamus in aggression control[81, 109], this suggests that adult consequences of early stressors may be attributed to both structural brain deficits and structural "gains".

Functional changes

Acute social challenges that elicit stress coping responses in rodents specifically and acutely activate the brain regions that promote aggressiveness, including the medial amygdala, mediobasal hypothalamus and dorsal aspects of the periaqueductal gray (PAG)[79]. By contrast, very early social stressors as well as social and non-social chronic stress in adulthood reduce activation in most areas of the social brain when subjects are exposed to other conspecifics[110-115], consistent with the general impairment in social behaviors induced by such stressors.

Experiencing stress chronically in adulthood or early in life results in alterations in cortico-limbic networks, including changes in amygdala-PFC connectivity[116]. Such changes are also frequently found in individuals with abnormal social behaviors[84]. In most such individuals frontal regions show reduced functioning. However, amygdala activation by emotional stimuli differs between subgroups of antisocial individuals: it shows hypofunctionality in individuals with psychopathic traits and hyperreactivity in those showing impulsive and reactive social problems[84]. Furthermore, carriers of genetic variants of serotonin-system-related genes that can, through an interaction with stress exposure, increase the development of impulsive aggression (see below), show increased reactivity in the amygdala and reduced reactivity in the emotion regulatory prefrontal regions (orbitofrontal and anterior cingulate cortices) during emotional arousal[117, 118]. Interestingly, peripubertal stress that reduces sociability and increases aggression in male rats also leads to amygdala hyperactivity and blunted activation of the medial orbitofrontal cortex when the rats encounter intruders in their home cage as adults[35]. Furthermore, alterations in the functional connectivity between the medial orbitofrontal cortex and the amygdala predicted the aggressive behavior of these mice[35]. However, animals exposed to post-weaning social isolation showed, as adults, activation of both the amygdala and orbitofrontal cortex in response to an intruder[119] (FIG. 1). This pattern may mimic findings in criminal psychopathic individuals, who showed enhanced PFC activation when punishing opponents in a competitive game[120].

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

Insights into brain changes that are associated with social abnormalities resulting from atypically low glucocorticoid levels were provided by studies in rats submitted to adrenalectomy and low dose corticosterone replacement. Strikingly, these animals show similar patterns of brain activation in response to encountering a conspecific towards which they displayed pathological aggression and during mouse killing (predatory aggression)[121, 122], suggesting that both stress-induced glucocorticoid levels and low basal and stress-activated glucocorticoids may be causally linked to abnormally high aggression. The activation of 'predatory circuits' when fights occur under low glucocorticoid levels may have its analog in human instrumental aggression, which — based on behavioral and emotional features — is often termed 'predatory' aggression, especially in the case of psychopathy[123].

Neurochemical mechanisms

Several neurotransmitter and neuropeptide systems were implicated in the effects of stress on social behaviors by neurobiological and pharmacological studies that found correlations between neurotransmitter or neuropeptide expression and effects of stress on social behavior and genetic studies exploring the interaction between specific genes and stress in the production of social dysfunctions.

Monoamines

Ample evidence from clinical and preclinical studies implicates the monoaminergic – particularly the serotonergic and dopaminergic – systems in the regulation of social behaviors. Stress experienced at different developmental periods can have persistent effects on the serotonergic system [such as changes in the expression of serotonin (5-HT) and its metabolites and receptors] and dopaminergic system in specific brain regions. Some studies have observed those changes in the context of increased aggression and reduced motivation for social exploration. For example, in rhesus monkeys, stress-induced increases in aggression were correlated with expression of the serotonin transporter (5-HTT) in infants[124] and inversely correlated with cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA; a metabolite of 5-HT) concentrations in adults[125]. In rats exposed to peripubertal stress, expression levels of both the monoamine oxidase A (MAOA, an enzyme that degrades monoamines) and 5HTT genes in the PFC were increased and this was accompanied by increased acetylation of histone H3 at the promoter of the MAOA gene[35]. Importantly, administration of a MAOA inhibitor in adulthood reversed the deficits in sociability and increased aggression in these rats[35]. Likewise, treatment with the serotonin reuptake inhibitor fluoxetine normalized changes in behaviour, biochemistry and cell firing in mice that were susceptible to the development of social aversion following social defeat stress[126, 127]. Interestingly, changes in the serotonergic system have also been detected in transgenerational studies of stress-induced social deficits[31]. Specifically, the offspring of male mice submitted to maternal separation and maternal stress showed social avoidance and altered social recognition memory, as well as reduced serotonin receptor 1A (5HT1A) expression in the dorsal raphe nucleus, and increased 5-HT levels in dorsal raphe projection areas[31].

Studies of social defeat in mice have suggested an involvement of the mesocorticolimbic dopaminergic system. Social defeat leads to reduced social exploration (social avoidance)[17] and a reduced probability of winning future social contests[128]. Social avoidance in such mice was associated with brain-derived neurotrophic factor (BDNF)-induced activation of the receptor tyrosine kinase TRKB signaling pathway in the nucleus accumbens (NAc)[127] and the activation of GRs in neurons expressing dopamine receptors[75]. Upregulation of phasic firing of dopamine neurons that project from the ventral tegmental area (VTA) to the NAc[127, 129] and decreased excitatory synaptic input to dopamine receptor D1-containing medium spiny neurons from the NAc[130] were also implicated in the development of social avoidance following exposure to social defeat.

Exposure to stressful experiences also frequently increases dopamine release or turnover in the NAc[131] and individual variation in VTA stress responses has been linked to individual differences

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

in coping responses to stress[127]. Moreover, sustained increases in dopaminergic activity in the NAc and activation of D1 receptors were also implicated in social defeat-induced social avoidance in both males and females from the monogamous California mouse (*Peromyscus californicus*) strain[132]. These enhanced DA responses might reflect animals' attempt to develop active coping responses to stressors, whereas inhibition of DA has been proposed to mediate passive coping with stressful situations appraised as unescapable and/or uncontrollable[133]. Accordingly, stress-related social subordination in rats has been associated with decreased dopamine transporter binding and increased D2 receptor binding[134].

Genetic association studies in human and non-human primates have identified polymorphisms in genes that regulate serotonin and dopaminergic neurotransmission as risk factors for the development of social dysfunctions, including pathological aggression. The *MAOA* gene was the first for which a gene-by-environment (specifically, maltreatment during early life) interaction was reported[135]. Subsequently, polymorphisms in the *5-HTT* gene were shown to contribute to individual differences in aggressiveness in individuals exposed to stress in early life[136], at the transition into adulthood[137] or acutely in adulthood[136, 138]. Genetic variants in dopamine-system-related genes are also associated with aggression. For example, a variant in the gene encoding dopamine receptor D2 (*DRD2*) was associated with social dysfunction in Vietnam veterans with PTSD[139]. Gene variants of the D4 receptor (*DRD4*), when combined with prenatal maternal stress, were associated with increased antisocial behavior in childhood[140] and increased aggression and low cortisol responses to social stress at adulthood[141].

Extrahypothalamic corticotropin releasing hormone (CRH)

Changes in the expression of components of the extrahypothalamic CRH system following stress and in the context of antisocial behaviors in humans and animals have been shown. They occur, for example, in patients with stress-related psychiatric disorders in which social behaviors are commonly compromised, such as anxiety and depression[142]. Abusive rhesus macaque mothers (who were abused themselves as infants) show higher CSF concentrations of CRH than controls and these are associated with antisocial behavior patterns[143]. The differences in the CRH system could be due to the early trauma or to genetic factors and findings in rats exposed to peripubertal stress indicate that early stress is a critical trigger. In these rats, social dysfunction was associated with enhanced CRH receptor 1 (*CRHR1*) expression in the hippocampus and the central nucleus of the amygdala, and treatment with a CRHR1 antagonist prevented the social dysfunctions[144]. Changes in the extrahypothalamic CRH system have also been observed after stress exposure in other developmental periods in rats[145,146] and prairie voles[147], but their role in the associated changes in social behavior has not been explored. Interestingly, antagonizing brain CRH receptors reduced acute stress-induced fighting in rats[148], decreased the expression of social defeat-induced submissive behavior in hamsters[149] and reversed passive stress coping behavior observed in male prairie voles separated from their female partners[150]. Overall, the highly stress-sensitive CRH system seems to play a central role in the regulation of a broad array of social behaviors[151].

Oxytocin and vasopressin

The neuropeptides arginine vasopressin and oxytocin, which are synthesized in the hypothalamus and limbic system modulating emotional behaviors (such as anxiety and depression), and multiple aspects of social behavior[152, 153]. Generally, evidence points to a role for vasopressin in promoting antisocial behaviors (such as aggression), whereas oxytocin facilitates prosocial actions (such as social affiliation, attachment, social support, maternal behavior and trust). Importantly, vasopressin tends to exert anxiogenic effects, whereas oxytocin exerts anxiolytic effects[152] and this difference probably contributes to the contrasting social actions of these neuropeptides[152].

Intriguingly, increases in both oxytocin and vasopressin release have been detected within hypothalamic and limbic brain regions following acute exposure to a variety of stressors[152].

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

Furthermore, in mandarin voles (*Microtus mandarimus*) paternal deprivation leading to impaired social recognition, was associated with a reduction in oxytocin receptors in the medial amygdala and nucleus accumbens[154].

Whether these modifications have a role in stress-related changes in social behaviors has been investigated. In one study, acute intracerebral administration of oxytocin reversed the social avoidance and reduced social preference elicited by prior social defeat stress in rodents[155]. In another study, a reduction in oxytocin receptor expression in the medial amygdala[156] was found in male rats that acquire a long-term subordinate status as a result of application of an acute stressor just before being exposed to a social contest against a non-stressed rat[157]. Long-term subordination was also induced in rats without former exposure to stress by microinfusion of an oxytocin receptor antagonist in the medial amygdala immediately after hierarchy formation[156], which suggests a role for the modulation of oxytocin receptors in stress-induced facilitation of long-term subordination. This view is in agreement with the findings of pharmacological experiments that implicated oxytocin in the medial amygdala in the establishment of social memories in rats[158].

Prenatal stress in rats both diminished the quality of social interactions at adulthood and resulted in alterations in the oxytocin system in the hypothalamus and amygdala: administration of oxytocin in these animals at adulthood reversed the social deficits[159]. Furthermore, enduring changes in the expression of oxytocin and vasopressin have been observed in adult rodents that had experienced maternal separation stress[160]. Pharmacological experiments showed that maternally-deprived male rats had a blunted vasopressin release within the septum when exposed to another male rat, and this was causally linked to their impaired social recognition memory[161]. In maternally separated female rats, a decrease in hypothalamic oxytocin immunoreactivity was found in the context of increased maternal aggression[42].

Lower oxytocin concentrations have also been observed in the CSF[162] and plasma[163] of women with a history of childhood abuse and borderline personality disorder. Interestingly, although a particular variation in the gene encoding the oxytocin receptor is generally associated with increased prosocial behavior, when it interacts with developmental stress it is associated with increased levels of antisocial behaviors[164].

Epigenetic mechanisms

An exploding body of evidence provides strong support for key roles of epigenetic mechanisms in mediating the effects of stress on brain and behavior, including gene-environment interactions at different developmental periods (for reviews, see[55, 165]). By regulating gene transcription, epigenetic mechanisms contribute to the effects of both stressors experienced in adulthood that have an immediate impact and those experienced early in life that have long-lasting effects on adult behavior and brain function. Following pioneering work that indicated that differential methylation of the GR gene mediated the effects of different mothering styles on stress responses and maternal behavior in rats[166], substantial evidence has shown that different components of the HPA axis are highly susceptible to epigenetic modulation by stress. Conversely, glucocorticoids themselves are important regulators of the epigenome[165]. Although the precise link with social behaviors is still scarce, the importance of these mechanisms in the link between stress and the social brain is illustrated by several examples. One study presented causal evidence for a role of epigenetic regulation of a Rho GTPase-related gene involved in the regulation of synaptic structure, RAC1, in the NAc in the development of social defeat stress-induced social avoidance[167]. Another study implicated acetylation of histone H3 at the promoter of the MAOA gene in long-lasting effects of peripuberty stress in the induction of antisocial behaviors at adulthood in rats[35]. Finally, a role for epigenetic mechanisms has also been suggested for the transmission of some behavioral stress effects across generations[57]. Future studies should more closely define the role of epigenetic modifications in the link between stress and the social brain.

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

Conclusions

A model of stress effects in the social brain

An emerging model suggests that social withdrawal in adulthood is a general consequence of experiencing, or having experienced, high and persistent stress levels, regardless of the developmental period (prenatal, early postnatal, juvenile, adulthood) when the episode occurs (FIG. 1). Similarly, aggression tends to be facilitated by stress (acute, chronic or developmental), unless the stress is inflicted by social defeat, which has an inhibitory effect on aggressive behavior. From a developmental perspective, stress appears to impose a progressive pattern of dysfunctional social behavior that begins with asociality (elicited by prenatal stressors) progresses to hostility (which emerges when stress is suffered postnatally) and ends with antisociality (which seems particularly bound to stress experienced in the juvenile period).

Although direct causality is not yet established, glucocorticoids seem to be particularly important mediators of stress effects. Their elevation during exposure to adversity contributes to the molecular changes – including alterations in expression of components of the monoaminergic and CRH systems, modulation of cell adhesion molecules and epigenetic modifications – that are associated with the alterations in neural structure and function and in inter-region connectivity induced by stress. In addition, long-term changes in the reactivity of glucocorticoid stress responses can also contribute to alterations in the processing of social information and/or ensuing social behaviors. Strikingly, both asociality and abnormal aggression can result from either blunted or enhanced glucocorticoid stress responses.

At the neural level, large changes in the social brain disrupt all aspects of sociality and consequently, lower the animals' ability to cope with social challenges. At one extreme, the 'asocial' profile (FIG. 1) is paralleled by volume reductions in major areas of the social brain when elicited by prenatal stress and involves profound alterations in the functioning of the mesolimbic system when resulting from chronic social defeat experiences at adulthood. Although the available data regarding the structural impact of different stress models in the social brain is limited, dendritic processes, spines and synapses tend to retract in brain regions involved in the processing of (social) information and executive control, but increase in regions involved in the processing of emotions. Changes in cell adhesion molecules (FIG. 3) parallel these structural effects, probably contributing to changes in the weight played by these different key brain areas in the processing of (social) information. Similar changes in circuit remodeling have been reported for chronic non-social stress and developmental conditions that exemplify the 'hostile' and 'antisocial' profiles (FIG. 1), although more information is needed to understand the specific changes for each profile. Another relevant emerging mechanism is an alteration in the neural E/I balance towards increased excitation and, again, a neural cell adhesion molecule (NLGN-2) appears to be a major stress-modulated target (FIG. 3). However, any emerging model is constrained by the rather incomplete and non-systematic data available which, beyond rendering the interpretation provided above tentative, also raises a series of outstanding questions.

Outstanding questions

Much progress still remains to be done to increase our understanding of how the social brain works and we are only starting to reveal how stress can interact with social brain function. Vulnerability factors – extensively studied in domains such as emotion and affect[168] – are poorly understood in the case of social behaviors. We have also not yet explored the possible effects of stress on the interaction between social and other domains. Interactions between the social and cognitive domains[169] appear particularly relevant in light of the proposed inverse relationship between the degree of abstract reasoning and violence[170] and correlations between working memory and abstract reasoning[171]. Another outstanding question is how stress influences the interaction

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

between social behavior and empathy. Although most current findings emphasize asocial and antisocial patterns of behaviors following stress, a few examples in humans indicate that stress can also facilitate prosocial behaviors by promoting altruism and empathy (BOX 1). This is important because although stress may help us "feel with others" undergoing similar stressful situations[172], very high stress seems to compromise empathic capacities [173-176]. Furthermore, there seems to be a bidirectional relationship between stress and social behaviors. Social integration and social support is an important modulator of individuals' stress reactivity and stress-related outcomes: positive social interactions buffer stress (BOX 5), whereas dysfunctional social interactions (such as being a victim of violence or having a subordinate role in highly unequal social hierarchies[177]) can trigger stress.

Clinical and societal implications

Some of the knowledge summarized here could have immediate applications: understanding the interaction between stress, the brain and social behavior may guide the development of novel treatment strategies. For example, neurochemical mechanisms that favor a prosocial attitude (such as oxytocin) might be used to develop pharmacological tools to reverse undesirable changes in neuronal communication that are caused by stress. Epigenetic mechanisms could be considered as alternative targets for intervention.

By affecting social behaviors, stress in an individual can have a multiplicative effect in society. Thus, stress is one of the key regulators not only of our social lives but also of the functioning of our societies. This opens novel avenues to potentially intervene in societal problems: would reducing stress levels and improving the stress reactions of individuals improve our social organizations? It is also important to consider the role of stress in the production of cycles of violence. If stress caused by social disputes – such as war, physical abuse or aberrant socioeconomic inequalities – exacerbates antisocial dispositions in individuals, it may be instrumental in the development of spirals of violence. Accordingly, tackling stress should also be considered as a promising strategy in conflict resolution programs. Another important dimension is the proposed role of stress in the transgenerational transmission of violence: this places a great responsibility on individuals, societies and political organizations to stop exposing today's children to excessive stress, violence or maltreatment. Given the recent growth in the number of studies into the interaction between stress and social behavior reviewed here, we are confident that this area of study will contribute with important solutions to the clinic and society.

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

Box 1. Stress and social behaviors in humans

Epidemiological studies. Several stress-eliciting factors have been related to high societal levels of crime and violence; these include high environmental temperature, which was found to correlate with violence in laboratory experiments[178]; income inequalities within regions and countries[8]; and economic crises, which particularly relate to high levels of violence against women and children[7].

Clinical studies. Insights into links between stress and social behaviors have also been obtained in studies of individuals with stress-related psychiatric disorders, such as posttraumatic stress disorder (PTSD) and depression. These disorders frequently involve marked dysfunctions in social functioning, including reductions in social motivation and social cognition, social anxiety and avoidance, alterations in social behaviors[9, 10], and high levels of anger, hostility or violence[179, 180], particularly when experiencing stress[181].

Adverse early-life social experiences are particularly associated with social anxiety and aggression later in life. Maltreatment during childhood, inflicted by family[182] or peers[183-185], is linked to social anxiety, impaired social skills and loneliness at adulthood[182], and is a robust predictor of adolescent and adult antisocial behaviors[186]. However, not all individuals are equally affected[187], which suggests that genetic factors interact with early adversity to mediate these effects[135, 186]. A direct causal effect of childhood adversity on aggression was suggested by findings from longitudinal twin studies[188]. Overall, these findings illustrate the concept of a 'cycle of violence' or intergenerational transmission of externalizing behaviors[189] observed in some families — through which maltreated children tend to become abusive parents — and that occurs for both general and domestic violence[190].

Psychosocial studies. Recently, the prosocial effects of stress have also been underscored through a series of studies that identified the phenomenon termed "altruism born of suffering"[191]. Specifically, these studies revealed increased motivation in former victims of suffering (whether from natural causes or inflicted by other human beings) to help others – particularly in-group members – and prevent further suffering[172, 191].

Behavioral economic studies. Several recent studies in this field also demonstrated prosocial effects of acute stress. In one example, shortly after being challenged with a standardized laboratory stressor male participants took economic decisions indicative of increased trust, trustworthiness, sharing[192] and altruistic punishment[193]. Other studies in civilian populations of countries engaged in war conflicts suggested that the well-known phenomenon of increased societal in-group cooperation in times of war might not be a direct, immediate reaction of the individuals but rather a result of group pressure[194] and early life programming[195].

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

Box 2. The palette of social behavioral tests in rodents

Social relationships in real-life situations in rodents involve sequences of behaviors. Several laboratory tests have been developed that allow these individual behaviors to be studied separately:

- The *three-chamber sociability test:* In this test, the subject is placed in a chamber adjacent to two other chambers (figure, part a). Each of these compartments contains a receptacle that allows an animal to see and smell, but not to directly contact, its content. One receptacle contains a conspecific animal and the other is empty or contains an inanimate object. The test monitors the percentage of time that the experimental animal spends exploring each receptacle.
- *Social memory tests* for recognition memory (figure, part b) compare the time an experimental animal spends exploring an unfamiliar animal versus the time it spends exploring a familiar animal (each animal is contained in a receptacle similar to that described above).
- The *social interaction test* (figure, part c) allows measurement of direct social interactions. It normally takes place in a neutral arena (to limit aggressiveness) and the propensity of unfamiliar individuals to engage in different forms of social interaction, including sniffing, following, and adjacent lying, is monitored
- The *resident/intruder test* (figure, part d) evaluates the aggressiveness of male rodents towards an intruder male placed into their territory. Quantitative measures of aggressive (offensive threats, bites) and defensive behaviors are monitored. In addition to assessing normal territorial aggression, this test can be used to detect antisocial features. Such features are identified as deviations from natural "rules" that govern aggressive behavior and that result from evolutionary pressures against dangerous forms of aggression[29]. These include excessive number of attacks (several folds larger than species-typical levels), attacks on non-threatening opponents (juveniles, females, or anesthetized animals), dangerous attacks targeting the head, throat and belly, deficits in social communication (failure/reluctance to communicate attack intentions by threats) and offensive ambiguity (such as parallel increases in offense and defense).
- *Social competition tests* (figure, part e) allow one to investigate the formation of social hierarchies and other social dynamics. These tests involve a visible burrow system[24] or observing two animals fighting for novel territory, food or water[157].

Each test focuses on one aspect of social behavior and can provide information complementary to the other tests. For example, whereas motivation might be to some degree masked by the actions of the opponent in the social interaction test, this limitation is precluded in the sociability chambers. However, actual social interactions are not observable in the latter. Likewise, aggressiveness is revealed in aggression tests but other types of social interactions are compromised.

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

Box 3. Early developmental stress procedures in rodents and their neuroendocrine effects

There are three developmental windows during which stressors elicit distinct and life-long changes in behavior: the prenatal period, during which stress mediators in the mother can reach the fetus via the placenta; the neonatal period, during which parent–pup interactions are particularly critical; and the juvenile period, during which the brain is still undergoing substantial developmental changes. The effects of exposure to stressors during these periods have been investigated in several rodent models (see the figure).

Prenatal stress: this model involves the exposure of dams to stressors (usually physical restraint) during pregnancy. The stressors are typically applied several times a day during the last week of pregnancy.
Maternal separation: this model involves the separation of the litter from the dam for more than 3 hours per day in the two weeks that follow birth.
Early social deprivation: in this model pups are separated from both the dam and their litter mates.
Post-weaning social isolation: this model involves the isolation rearing of subjects from weaning until early adulthood.
Early subjugation: this model consists of repeated defeats of a young rat or mouse (typically between postnatal days (PND) 28-42) by an aggressive adult male.
Peripubertal stress: this model involves the exposure of a young rat or mouse (typically between postnatal days 28-42) to a variety of non-social stressors.

Each of these procedures – which are typically administered in an unpredictable and uncontrollable manner – increases glucocorticoid production acutely (except social isolation), but their long-term effects on the hypothalamic-pituitary-adrenal (HPA) axis differ (see the figure; arrows indicate HPA-axis function in adulthood for early stressors, and in non-stress periods for adult stressors). Prenatal stress, maternal separation and post-weaning social isolation lead to increased HPA-axis activity (either or both under basal conditions and in response to stress) in adulthood[65, 196, 197]. By contrast, early deprivation, early subjugation and peripubertal stressors lead to decreased HPA-axis activity in adulthood[35, 39, 64, 66]. The differences in the long term effects induced by the maternal separation and early deprivation models depend only on the social context of stress administration (that is, whether maternally separated animals remain with peers or isolated)[198].

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

Box 4. Stress, cell adhesion molecules and the balance excitation/inhibition (E/I)

Stress-induced changes in social behaviors involve a reduction in specific cell adhesion molecules that play key roles in the remodeling of neural circuits, synaptic function and in the balance between neural excitation and inhibition.

The neural cell adhesion molecule (NCAM) is down-regulated by chronic stress in the hippocampus and prefrontal cortex[199] [figure, part a]. Mice with a forebrain-specific NCAM deletion display increased vulnerability to the development of aggressive behaviors when repeatedly exposed to uncontrollable stressors[200].

A reduction in nectin-3 participates in structural and functional alterations that occur in the hippocampus following stress[108], including reductions in social exploration and social recognition[14]. Although the hippocampus is not classically included among the brain regions that are at the core of the social brain, it exerts direct and indirect influences on the brain structures that control social behaviors[201]. Hippocampal expression of nectin-3 is reduced following chronic restrain stress in rats and was implicated in the induced. Down-regulation of nectin-3 by chronic stress involves proteolytic cleavage by matrix metalloproteinase MMP-9, which is elicited through NMDA receptor activation[14] [figure, part b].

Neuroligins (NLGNs) are involved in the regulation of the neural excitation/inhibition (E/I) balance and social behaviors[202]. NLGN-1 has a key role in the functioning of excitatory synapses and NLGN-2 has a similar role at inhibitory synapses[202]. Alterations in the neural E/I balance[203,204] are believed to underlie social deficits in psychiatric disorders, and chronic stress was shown to lead to an increase in the E/I balance[205,206,207] in the hippocampus of rodents. Chronic stress reduces NLGN-2, but not NLGN-1, expression throughout the hippocampus in parallel with decreased sociability and increased aggression in rats[13] [figure, part c]. Hippocampal overexpression of NLGN-2 reduced aggressive behavior in rats[208].

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

Box 5. Social buffering of stress in rodents: effects and mechanisms

Social interactions can protect individuals from exerting exaggerated physiological stress responses to challenging situations, and consequently prevent the development of stress-related pathologies[209]. Although this phenomenon is well-known in humans, several studies have confirmed its existence in animals and have started searching for the underlying neurobiological mechanisms. Oxytocin's actions in the brain reduce stress-induced corticosterone release and anxiety behavior in rodents[210] and oxytocin was also shown to be a key player in the social buffering of stress. Oxytocin release within the paraventricular nucleus of the hypothalamus, triggered by mating, mediated mating-induced anxiolytic behavior in male rats[211]. Oxytocin release that was independent of mating was involved in the buffering of stress-induced increases in anxiety-like behaviors and circulating corticosterone that occur in female prairie voles if the male partner is present[212]. Furthermore, social buffering in rats was also shown to protect from the development of alterations in social interactions that otherwise emerge following stress exposure[213].

Social buffering by mothers and peers can also protect against effects induced by early-life stress. For example, rat pups deprived of their mother's presence for a few hours have a fearful phenotype in adulthood, but only if they were also isolated from peers[214]. Moreover, mother-infant interactions are essential determinants of a pup's corticosterone responses to stressful stimuli during early life and influence the extent to which early-life stress affects behavior and emotionality in adulthood[215, 216]. In infants, changes in cortical synchrony (i.e., the level of synchronization of neural oscillations at particular frequencies, a fundamental mechanisms for enabling coordinated neural activity and essential for brain development) may be modulated by maternal contact[217], and this might be a mechanism through which mother-infant interactions can affect circuit development.

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

Glossary

Stress response: The activation of coordinated neurophysiological responses in the brain and periphery – i.e., sympathetic nervous system and hypothalamus-pituitary-adrenal (HPA) axis – to restore homeostasis disturbed by environmental demands or 'stressors'.

Stressors: Noxious stimuli eliciting a stress response.

Behavioral agitation: Rapid switches from one behavior to the other, included running around the perimeter of the cage, jumping, repeated self-grooming, and/or performing repeated, stereotypy-like behaviors.

Offensive ambiguity: Increased aggression against small, but decreased aggression against large opponents, as well as increased defensiveness on the background of increased offensiveness.

Agonistic behavior: Any social behaviour related to fighting. It includes threats, displays, retreats, placating aggressors, and conciliation.

Antisociality: Agonistic behaviors that brake evolutionarily-shaped behavioral "rules" that limit dangerous forms of aggression. It includes excessive levels and displaced targeting of attack and deficient social communication.

Epigenetic mechanisms: Changes in gene expression that do not arise from changes to the DNA sequence and that include alterations in DNA methylation, histone modifications, and noncoding RNAs (microRNAs and long noncoding RNAs).

Behavioral economics: A research field that investigates social behaviors by applying economic games to participants that are asked to take decisions that will have an impact on the payoffs received by other player/s and themselves.

Conspecifics: Individuals of the same species

Social defeat: Losing and aggressive encounter, which is behaviorally identified by submissive postures shown in response to offense by the winner and by the avoidance of social contacts and aggression.

Instrumental aggression: Premeditated aggressive action that has a specific goal e.g. material gain. It is associated with low emotional and physiological arousal, which mainly characterizes animal analogs.

Extrahypothalamic CRH system: Neurons containing CRH and/or CRH receptors whose cell bodies are localized in other brain regions beyond the hypothalamus.

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

Acknowledgements

This study was supported by grants from the Swiss National Science Foundation (31003AB-135710 and 31003A_152614; the NCCR 'The synaptic basis of mental diseases'), the Oak Foundation, the European Union (MEMSTICK Project, FP7-HEALTH-F2M-2007-201600) and intramural funding from the EPFL to CS and ERC-2011-ADG-294313 (SERRACO) grant to JH. The authors thank members from their respective laboratories for their original scientific contributions to the work reviewed here.

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

Legends for figures

Figure 1. **Social behavioral profiles emerging in response to stress exposure.** We can distinguish four different patterns of behavioural change that result from exposure to different types of stressor at different developmental time points. In profile A (green), acute stressors activate coping mechanisms and transiently promote agonistic behavior, including antisocial features. This profile is characterized by a transient shift towards aggressiveness ('fight or flight' changes). In Profile B (blue), prenatal stressors and chronic social defeat in adulthood promote passive coping mechanisms (including signs of anxiety and depression) along with a general reduction of social behaviors (asociality) without inducing abnormal forms of aggression; In profile C (brown), maternal separation and chronic physical stressors administered in adulthood result in behavioral withdrawal in all contexts except for aggression, which increases (these animals are classified as hostile, anxious and/ or depressed); In profile D (red), early social deprivation and stress experienced during the juvenile period induce a behavioral profile marked by different signs of antisociality. These animals are characterized by abnormal forms of aggression and model-dependent changes in other behaviors. *PS*, prenatal stress; *MS*, maternal separation; *ED*, early deprivation; *ES*, early subjugation; *pPS*, non-social peripubertal stressors; *pwSI*, post-weaning social isolation; *CHphS*, chronic physical stress; *CHsS*, chronic social defeat stress; *AcS*, acute stress. Horizontal arrows mean no changes.

Figure 2. The social brain in humans and animals. The left-hand panel illustrates the brain regions that have become known as the 'social brain' in humans as a result of neuroimaging studies. The right-hand panel depicts areas that constitute the "aggressive brain" in rodents on the basis of stimulation, lesion, and immunocytochemical studies[79, 81, 109]. Although the techniques employed in identifying these brain aras were different, and the behaviors that they control are overlapping but distinct, similarities between the identified brain regions involved in the social brain in humans and the aggressive brain in rodents are noticeable. *arrows*, the proposed flow of information between areas; *brackets*; modulating inputs affecting multiple brain sites; *VTA*, ventral tegmental area; *nACC*, nucleus accumbens; *vPALL*, ventral pallidum; *PAG*, periaqueductal gray; *5-HT*, serotonin, *DA*, dopamine; *AVP*, vasopressin, *OT*, oxytocin).

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

Reference List

1. de Kloet, E.R., Joels, M. & Holsboer, F. Stress and the brain: from adaptation to disease. *Nature reviews. Neuroscience* **6**, 463-75 (2005).
2. Joels, M. & Baram, T.Z. The neuro-symphony of stress. *Nat Rev Neurosci* **10**, 459-66 (2009).
3. Ulrich-Lai, Y.M. & Herman, J.P. Neural regulation of endocrine and autonomic stress responses. *Nat Rev Neurosci* **10**, 397-409 (2009).
4. Lupien, S.J., McEwen, B.S., Gunnar, M.R. & Heim, C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat Rev Neurosci* **10**, 434-45 (2009).

This is an excellent account on the effects of stress suffered accross the life-span and its impact on brain development, function and the emergence of psychiatric vulnerabilities. In some respects, this is the "non-social counterpart" of the present review.

5. McEwen, B.S. The ever-changing brain: cellular and molecular mechanisms for the effects of stressful experiences. *Dev Neurobiol* **72**, 878-90 (2012).
6. Cannon, W.B. Bodily Changes in Pain, Hunger, Fear and Rage: An Account of Recent Researches into the Function of Emotional Excitement. *Appleton, New York* (1915).
7. Burkle, F.M., Jr., Argent, A.C., Kissoon, N. & Task Force for Pediatric Emergency Mass Critical, C. The reality of pediatric emergency mass critical care in the developing world. *Pediatr Crit Care Med* **12**, S169-79 (2011).
8. Wilkinson, R. Why is violence more common where inequality is greater? *Ann N Y Acad Sci* **1036**, 1-12 (2004).
9. Nemeroff, C.B. & Vale, W.W. The neurobiology of depression: inroads to treatment and new drug discovery. *J Clin Psychiatry* **66 Suppl 7**, 5-13 (2005).
10. Kennedy, D.P. & Adolphs, R. The social brain in psychiatric and neurological disorders. *Trends Cogn Sci* **16**, 559-72 (2012).
11. de Almeida, R.M. & Miczek, K.A. Aggression escalated by social instigation or by discontinuation of reinforcement ("frustration") in mice: inhibition by anpirtoline: a 5-HT1B receptor agonist. *Neuropsychopharmacology* **27**, 171-81 (2002).
12. Takahashi, A. et al. Behavioral characterization of escalated aggression induced by GABA(B) receptor activation in the dorsal raphe nucleus. *Psychopharmacology (Berl)* **224**, 155-66 (2012).
13. van der Kooij, M.A. et al. Impaired hippocampal neuroligin-2 function by chronic stress or synthetic peptide treatment is linked to social deficits and increased aggression. *Neuropsychopharmacology* **39**, 1148-58 (2014).
14. van der Kooij, M.A. et al. Role for MMP-9 in stress-induced downregulation of nectin-3 in hippocampal CA1 and associated behavioural alterations. *Nat Commun* **5** (2014). **This study implicates a new molecular cascade in the hippocampus mediating the effects of chornic stress in sociability and cognition.**
15. Wood, G.E., Young, L.T., Reagan, L.P. & McEwen, B.S. Acute and chronic restraint stress alter the incidence of social conflict in male rats. *Horm Behav* **43**, 205-13 (2003).
16. Castro, J.E. et al. Personality traits in rats predict vulnerability and resilience to developing stress-induced depression-like behaviors, HPA axis hyper-reactivity and brain changes in pERK1/2 activity. *Psychoneuroendocrinology* **37**, 1209-23 (2012).
17. Berton, O. et al. Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. *Science* **311**, 864-8 (2006).
18. Van den Berg, C.L. et al. Isolation changes the incentive value of sucrose and social behaviour in juvenile and adult rats. *Behav Brain Res* **106**, 133-42 (1999).

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

19. Harris, B.N., de Jong, T.R., Yang, V. & Saltzman, W. Chronic variable stress in fathers alters paternal and social behavior but not pup development in the biparental California mouse (Peromyscus californicus). *Horm Behav* **64**, 799-811 (2013).
20. Mineur, Y.S., Prasol, D.J., Belzung, C. & Crusio, W.E. Agonistic behavior and unpredictable chronic mild stress in mice. *Behav Genet* **33**, 513-9 (2003).
21. Yohe, L.R., Suzuki, H. & Lucas, L.R. Aggression is suppressed by acute stress but induced by chronic stress: immobilization effects on aggression, hormones, and cortical 5-HT(1B)/ striatal dopamine D(2) receptor density. *Cogn Affect Behav Neurosci* **12**, 446-59 (2012).
22. Malick, J.B. The pharmacology of isolation-induced aggressive behavior in mice. *Curr Dev Psychopharmacol* **5**, 1-27 (1979).
23. Beerda, B., Schilder, M.B., van Hooff, J.A., de Vries, H.W. & Mol, J.A. Chronic stress in dogs subjected to social and spatial restriction. I. Behavioral responses. *Physiol Behav* **66**, 233-42 (1999).
24. Blanchard, D.C. et al. Visible Burrow System as a Model of Chronic Social Stress - Behavioral and Neuroendocrine Correlates. *Psychoneuroendocrinology* **20**, 117-134 (1995).
25. Hsu, Y., Earley, R.L. & Wolf, L.L. Modulation of aggressive behaviour by fighting experience: mechanisms and contest outcomes. *Biol Rev Camb Philos Soc* **81**, 33-74 (2006).
26. Huhman, K.L. et al. Conditioned defeat in male and female Syrian hamsters. *Horm Behav* **44**, 293-9 (2003).
27. Potegal, M., Huhman, K., Moore, T. & Meyerhoff, J. Conditioned defeat in the Syrian golden hamster (Mesocricetus auratus). *Behav Neural Biol* **60**, 93-102 (1993).
28. Nephew, B.C. & Bridges, R.S. Effects of chronic social stress during lactation on maternal behavior and growth in rats. *Stress* **14**, 677-84 (2011).
29. Miczek, K.A., de Boer, S.F. & Haller, J. Excessive aggression as model of violence: a critical evaluation of current preclinical methods. *Psychopharmacology* **226**, 445-458 (2013).

This study updates the criteria based on which antisocial features can be differentiated in animals, presents in detail three such models and evaluates their translational value for understanding human violence.

30. de Souza, M.A. et al. Prenatal stress produces social behavior deficits and alters the number of oxytocin and vasopressin neurons in adult rats. *Neurochem Res* **38**, 1479-89 (2013).
31. Franklin, T.B., Linder, N., Russig, H., Thony, B. & Mansuy, I.M. Influence of early stress on social abilities and serotonergic functions across generations in mice. *PLoS One* **6**, e21842 (2011).

This is the first study that shows that early life stress can change social behavior in individuals across generations.

32. Yu, P. et al. Early social deprivation impairs pair bonding and alters serum corticosterone and the NAcc dopamine system in mandarin voles. *Psychoneuroendocrinology* **38**, 3128-3138 (2013).
33. Naert, A., Callaerts-Vegh, Z. & D'Hooge, R. Nocturnal hyperactivity, increased social novelty preference and delayed extinction of fear responses in post-weaning socially isolated mice. *Brain Research Bulletin* **85**, 354-362 (2011).
34. Vidal, J., Buwalda, B. & Koolhaas, J.M. Male Wistar rats are more susceptible to lasting social anxiety than Wild-type Groningen rats following social defeat stress during adolescence. *Behavioural processes* **88**, 76-80 (2011).
35. Márquez, C. et al. Peripuberty stress leads to abnormal aggression, altered amygdala and orbitofrontal reactivity and increased prefrontal MAOA gene expression. *Transl Psychiatry* **3**, e216 (2013).

This study presents strong evidence for a role of neurobiological mechanisms in the link from early adversity to antisocial behaviors, and shows that animal models recapitulate changes in brain function that resemble those of individuals with borderline personality disorder.

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

36. Wei, B. et al. Neonatal tactile stimulation alleviates the negative effects of neonatal isolation on novel object recognition, sociability and neuroendocrine levels in male adult mandarin voles (Microtus mandarinus). *Physiol Behav* **112-113**, 14-22 (2013).
37. Jia, R., Tai, F., An, S., Zhang, X. & Broders, H. Effects of neonatal paternal deprivation or early deprivation on anxiety and social behaviors of the adults in mandarin voles. *Behav Processes* **82**, 271-8 (2009).
38. Workman, J.L., Fonken, L.K., Gusfa, J., Kassouf, K.M. & Nelson, R.J. Post-weaning environmental enrichment alters affective responses and interacts with behavioral testing to alter nNOS immunoreactivity. *Pharmacol Biochem Behav* **100**, 25-32 (2011).
39. Wommack, J.C., Salinas, A., Melloni, R.H., Jr. & Delville, Y. Behavioural and neuroendocrine adaptations to repeated stress during puberty in male golden hamsters. *J Neuroendocrinol* **16**, 767-75 (2004).
40. Shimozuru, M., Kikusui, T., Takeuchi, Y. & Mori, Y. Effects of isolation-rearing on the development of social behaviors in male Mongolian gerbils (Meriones unguiculatus). *Physiol Behav* **94**, 491-500 (2008).
41. Patin, V., Lordi, B., Vincent, A. & Caston, J. Effects of prenatal stress on anxiety and social interactions in adult rats. *Brain Res Dev Brain Res* **160**, 265-74 (2005).
42. Veenema, A.H., Bredewold, R. & Neumann, I.D. Opposite effects of maternal separation on intermale and maternal aggression in C57BL/6 mice: link to hypothalamic vasopressin and oxytocin immunoreactivity. *Psychoneuroendocrinology* **32**, 437-50 (2007).
43. Veenema, A.H., Blume, A., Niederle, D., Buwalda, B. & Neumann, I.D. Effects of early life stress on adult male aggression and hypothalamic vasopressin and serotonin. *Eur J Neurosci* **24**, 1711-20 (2006).

This study was the first one that, in rodents, showed that early life adversity can lead to increased aggression, and identified changes in social neuropetides and serotonin as potential mediators.

44. Day, H.D., Seay, B.M., Hale, P. & Hendricks, D. Early social deprivation and the ontogeny of unrestricted social behavior in the laboratory rat. *Dev Psychobiol* **15**, 47-59 (1982).
45. Cunningham, R.L. & McGinnis, M.Y. Prepubertal social subjugation and anabolic androgenic steroid-induced aggression in male rats. *J Neuroendocrinol* **20**, 997-1005 (2008).
46. Cumming, M.J., Thompson, M.A. & McCormick, C.M. Adolescent social instability stress increases aggression in a food competition task in adult male Long-Evans rats. *Dev Psychobiol* **56**, 1575-88 (2014).
47. Toth, M., Halasz, J., Mikics, E., Barsy, B. & Haller, J. Early social deprivation induces disturbed social communication and violent aggression in adulthood. *Behav Neurosci* **122**, 849-54 (2008).
48. Cordero, M.I. et al. Evidence for biological roots in the transgenerational transmission of intimate partner violence. *Transl Psychiatry* **2**, e106 (2012).
49. Delville, Y., Melloni, R.H. & Ferris, C.F. Behavioral and neurobiological consequences of social subjugation during puberty in golden hamsters. *Journal of Neuroscience* **18**, 2667-2672 (1998).
50. Wommack, J.C., Taravosh-Lahn, K., David, J.T. & Delville, Y. Repeated exposure to social stress alters the development of agonistic behavior in male golden hamsters. *Hormones and Behavior* **43**, 229-236 (2003).
51. Hollis, F., Isgor, C. & Kabbaj, M. The consequences of adolescent chronic unpredictable stress exposure on brain and behavior. *Neuroscience* **249**, 232-41 (2013).
52. Zimmerberg, B. & Sageser, K.A. Comparison of two rodent models of maternal separation on juvenile social behavior. *Front Psychiatry* **2**, 39 (2011).

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

53. Kempes, M.M., Gulickx, M.M., van Daalen, H.J., Louwerse, A.L. & Sterck, E.H. Social competence is reduced in socially deprived rhesus monkeys (Macaca mulatta). *J Comp Psychol* **122**, 62-7 (2008).
54. Gluckman, P.D., Hanson, M.A. & Beedle, A.S. Early life events and their consequences for later disease: A life history and evolutionary perspective. *American Journal of Human Biology* **19**, 1-19 (2007).
55. Provencal, N. & Binder, E.B. The effects of early life stress on the epigenome: From the womb to adulthood and even before. *Exp Neurol* (2014).
56. Babb, J.A., Carini, L.M., Spears, S.L. & Nephew, B.C. Transgenerational effects of social stress on social behavior, corticosterone, oxytocin, and prolactin in rats. *Horm Behav* **65**, 386-93 (2014).
57. Gapp, K., von Ziegler, L., Tweedie-Cullen, R.Y. & Mansuy, I.M. Early life epigenetic programming and transmission of stress-induced traits in mammals: how and when can environmental factors influence traits and their transgenerational inheritance? *Bioessays* **36**, 491-502 (2014).
58. de Kloet, E.R., Karst, H. & Joels, M. Corticosteroid hormones in the central stress response: Quick-and-slow. *Frontiers in Neuroendocrinology* **29**, 268-272 (2008).
59. Haller, J., Mikics, E. & Makara, G.B. The effects of non-genomic glucocorticoid mechanisms on bodily functions and the central neural system. A critical evaluation of findings. *Frontiers in Neuroendocrinology* **29**, 273-291 (2008).
60. Groeneweg, F.L., Karst, H., de Kloet, E.R. & Joels, M. Mineralocorticoid and glucocorticoid receptors at the neuronal membrane, regulators of nongenomic corticosteroid signalling. *Mol Cell Endocrinol* **350**, 299-309 (2012).
61. Makara, G.B. & Haller, J. Non-genomic effects of glucocorticoids in the neural system - Evidence, mechanisms and implications. *Progress in Neurobiology* **65**, 367-390 (2001).
62. Meaney, M.J. et al. Early environmental regulation of forebrain glucocorticoid receptor gene expression: Implications for adrenocortical responses to stress. *Developmental Neuroscience* **18**, 49-72 (1996).
63. Welberg, L.A.M. & Seckl, J.R. Prenatal stress, glucocorticoids and the programming of the brain. *Journal of Neuroendocrinology* **13**, 113-128 (2001).
64. Rees, S.L., Steiner, M. & Fleming, A.S. Early deprivation, but not maternal separation, attenuates rise in corticosterone levels after exposure to a novel environment in both juvenile and adult female rats. *Behavioural Brain Research* **175**, 383-391 (2006).

This study is important because it showed for the first time that apparently minor technical details of stress exposure have substantial impact on the long-term consequences of stressors. Particularly, the authors directly compared the maternal separation and early deprivation models (neonatal separation from the dam and from both the dam and cage-mates, respectively).

65. Toth, M., Mikics, E., Tulogdi, A., Aliczki, M. & Haller, J. Post-weaning social isolation induces abnormal forms of aggression in conjunction with increased glucocorticoid and autonomic stress responses. *Hormones and Behavior* **60**, 28-36 (2011).
66. Leshner, A.I. & Schwartz, S.M. Neonatal Corticosterone Treatment Increases Submissiveness in Adulthood in Mice. *Physiology & Behavior* **19**, 163-165 (1977).
67. Veenit, V., Cordero, M.I. & Sandi, C. Increased corticosterone in peripubertal rats leads to long-lasting alterations in social exploration and aggression. *Front Behav Neuroscience* **7** (2013).
68. Poirier, G., Imamura, N., Zanoletti, O. & Sandi, C. Social deficits induced by peripubertal stress in rats are reversed by resveratrol. *J Psychiatr Res* **in press** (2014).

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

69. Tzanoulinou, S., Riccio, O., de Boer, M.W. & Sandi, C. Peripubertal stress-induced behavioral changes are associated with altered expression of genes involved in excitation and inhibition in the amygdala. *Transl Psychiatry* **4**, e410 (2014).
70. Tzanoulinou, S. et al. Long-Term Behavioral Programming Induced by Peripuberty Stress in Rats Is Accompanied by GABAergic-Related Alterations in the Amygdala. *Plos One* **9**, e94666 (2014).
71. Mikics, É., Kruk, M.R. & Haller, J. Genomic and non-genomic effects of glucocorticoids on aggressive behavior in male rats. *Psychoneuroendocrinology* **29**, 618-635 (2004).
72. Haller, J. & Kruk, M.R. Normal and abnormal aggression: human disorders and novel laboratory models. *Neuroscience and Biobehavioral Reviews* **30**, 292-303 (2006).
73. File, S.E., Vellucci, S.V. & Wendlandt, S. Corticosterone -- an anxiogenic or an anxiolytic agent? *J Pharm Pharmacol* **31**, 300-5 (1979).
74. Haller, J., van de Schraaf, J. & Kruk, M.R. Deviant forms of aggression in glucocorticoid hyporeactive rats: A model for 'pathological' aggression? *Journal of Neuroendocrinology* **13**, 102-107 (2001).

This was the first study demonstrating that the inhibition of glucocorticoid production induces qualitative changes in aggressive behavior, proposed that these changes were abnormal, and model aspects of human violence. It was also the first to propose criteria for differentiating normal and abnormal forms of attack in rodents.

75. Barik, J. et al. Chronic stress triggers social aversion via glucocorticoid receptor in dopaminoceptive neurons. *Science* **339**, 332-5 (2013).
76. Bevilacqua, L. et al. Interaction between FKBP5 and childhood trauma and risk of aggressive behavior. *Arch Gen Psychiatry* **69**, 62-70 (2012).
77. Buchmann, A.F. et al. Moderating role of FKBP5 genotype in the impact of childhood adversity on cortisol stress response during adulthood. *Eur Neuropsychopharmacol* **24**, 837-45 (2014).
78. Klengel, T. et al. Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. *Nat Neurosci* **16**, 33-41 (2013).
79. Insel, T.R. & Fernald, R.D. How the brain processes social information: Searching for the social brain. *Annual Review of Neuroscience* **27**, 697-722 (2004).

This is the first review explicitely focusing on the concept of social brain. It analyses socially relevant neural systems from animals to humans. The review encompasses all aspects of social behavior from perception to action.

80. Kas, M.J., Modi, M.E., Saxe, M.D. & Smith, D.G. Advancing the discovery of medications for autism spectrum disorder using new technologies to reveal social brain circuitry in rodents. *Psychopharmacology* **231**, 1147-1165 (2014).
81. Siegel, A., Roeling, T.A.P., Gregg, T.R. & Kruk, M.R. Neuropharmacology of brain-stimulation-evoked aggression. *Neuroscience and Biobehavioral Reviews* **23**, 359-389 (1999).
82. Yu, R.J., Mobbs, D., Seymour, B., Rowe, J.B. & Calder, A.J. The neural signature of escalating frustration in humans. *Cortex* **54**, 165-178 (2014).
83. White, S.F., Brislin, S.J., Sinclair, S. & Blair, J.R. Punishing unfairness: rewarding or the organization of a reactively aggressive response? *Hum Brain Mapp* **35**, 2137-47 (2014).
84. Glenn, A.L. & Raine, A. Neurocriminology: implications for the punishment, prediction and prevention of criminal behaviour. *Nat Rev Neurosci* **15**, 54-63 (2014).
85. Bruhl, A.B. et al. Increased cortical thickness in a frontoparietal network in social anxiety disorder. *Hum Brain Mapp* **35**, 2966-77 (2014).
86. Blair, R.J. Dysfunctions of medial and lateral orbitofrontal cortex in psychopathy. *Ann N Y Acad Sci* **1121**, 461-79 (2007).
87. Gudsnuk, K. & Champagne, F.A. Epigenetic influence of stress and the social environment. *ILAR J* **53**, 279-88 (2012).

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

88. Johnson, M.H., Grossmann, T. & Cohen Kadosh, K. Mapping functional brain development: Building a social brain through interactive specialization. *Dev Psychol* **45**, 151-9 (2009).
89. McEwen, B.S. Allostasis and allostatic load: implications for neuropsychopharmacology. *Neuropsychopharmacology* **22**, 108-24 (2000).
90. Buss, C., Davis, E.P., Muftuler, L.T., Head, K. & Sandman, C.A. High pregnancy anxiety during mid-gestation is associated with decreased gray matter density in 6-9-year-old children. *Psychoneuroendocrinology* **35**, 141-53 (2010).
91. Sandman, C.A. & Davis, E.P. Neurobehavioral risk is associated with gestational exposure to stress hormones. *Expert Rev Endocrinol Metab* **7**, 445-459 (2012).
92. Tobe, I. et al. Effects of repeated maternal stress on FOS expression in the hypothalamic paraventricular nucleus of fetal rats. *Neuroscience* **134**, 387-95 (2005).
93. Fujioka, T. et al. The effects of prenatal stress on the development of hypothalamic paraventricular neurons in fetal rats. *Neuroscience* **92**, 1079-88 (1999).
94. Mychasiuk, R., Gibb, R. & Kolb, B. Prenatal bystander stress induces neuroanatomical changes in the prefrontal cortex and hippocampus of developing rat offspring. *Brain Res* **1412**, 55-62 (2011).
95. Zuloaga, D.G. et al. Perinatal dexamethasone-induced alterations in apoptosis within the hippocampus and paraventricular nucleus of the hypothalamus are influenced by age and sex. *J Neurosci Res* **90**, 1403-12 (2012).
96. McEwen, B.S. Stress, sex, and neural adaptation to a changing environment: mechanisms of neuronal remodeling. *Annals of the New York Academy of Sciences* **1204 Suppl**, E38-59 (2010).
97. Sapolsky, R.M. Stress and plasticity in the limbic system. *Neurochem Res* **28**, 1735-42 (2003).
98. Wellman, C.L. Dendritic reorganization in pyramidal neurons in medial prefrontal cortex after chronic corticosterone administration. *J Neurobiol* **49**, 245-53 (2001).
99. Baudin, A. et al. Maternal deprivation induces deficits in temporal memory and cognitive flexibility and exaggerates synaptic plasticity in the rat medial prefrontal cortex. *Neurobiol Learn Mem* **98**, 207-14 (2012).
100. Brenhouse, H.C., Lukkes, J.L. & Andersen, S.L. Early life adversity alters the developmental profiles of addiction-related prefrontal cortex circuitry. *Brain Sci* **3**, 143-58 (2013).
101. Chocyk, A. et al. Early-life stress affects the structural and functional plasticity of the medial prefrontal cortex in adolescent rats. *Eur J Neurosci* **38**, 2089-107 (2013).
102. Cooke, B.M., Chowanadisai, W. & Breedlove, S.M. Post-weaning social isolation of male rats reduces the volume of the medial amygdala and leads to deficits in adult sexual behavior. *Behav Brain Res* **117**, 107-13 (2000).
103. Schubert, M.I., Porkess, M.V., Dashdorj, N., Fone, K.C. & Auer, D.P. Effects of social isolation rearing on the limbic brain: a combined behavioral and magnetic resonance imaging volumetry study in rats. *Neuroscience* **159**, 21-30 (2009).
104. Bastida, C.C. et al. Chronic social stress in puberty alters appetitive male sexual behavior and neural metabolic activity. *Horm Behav* **66**, 220-7 (2014).
105. Buwalda, B., Stubbendorff, C., Zickert, N. & Koolhaas, J.M. Adolescent social stress does not necessarily lead to a compromised adaptive capacity during adulthood: a study on the consequences of social stress in rats. *Neuroscience* **249**, 258-70 (2013).
106. Weathington, J.M., Strahan, J.A. & Cooke, B.M. Social experience induces sex-specific fos expression in the amygdala of the juvenile rat. *Horm Behav* **62**, 154-61 (2012).
107. Irles, C., Nava-Kopp, A.T., Moran, J. & Zhang, L. Neonatal maternal separation up-regulates protein signalling for cell survival in rat hypothalamus. *Stress* **17**, 275-84 (2014).

Whereas most studies focus on brain disfunctions that develop in the prefrontal cortex and amygdala, this interesting report reveals that early stressors promote cell survival, suppress cell death, and increase cell density in the hypothalamus, an important locus of

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

control of aggressiveness. It suggests that disrupted sociality can not only ensue from deficits in brain circuits that control cognitive and emotional functions, but also from structural "gains" in areas that are involved in the execution of behavioral acts.

108. Wang, H. & Gondre-Lewis, M.C. Prenatal nicotine and maternal deprivation stress de-regulate the development of CA1, CA3, and dentate gyrus neurons in hippocampus of infant rats. *PLoS One* **8**, e65517 (2013).
109. Haller, J. The neurobiology of abnormal manifestations of aggression--a review of hypothalamic mechanisms in cats, rodents, and humans. *Brain Res Bull* **93**, 97-109 (2013).
110. Desbonnet, L., Garrett, L., Daly, E., McDermott, K.W. & Dinan, T.G. Sexually dimorphic effects of maternal separation stress on corticotrophin-releasing factor and vasopressin systems in the adult rat brain. *Int J Dev Neurosci* **26**, 259-68 (2008).
111. Humm, J.L., Lambert, K.G. & Kinsley, C.H. Paucity of c-fos expression in the medial preoptic area of prenatally stressed male rats following exposure to sexually receptive females. *Brain Res Bull* **37**, 363-8 (1995).
112. Jahng, J.W. et al. Mesolimbic dopaminergic activity responding to acute stress is blunted in adolescent rats that experienced neonatal maternal separation. *Neuroscience* **171**, 144-52 (2010).
113. Chung, K.K., Martinez, M. & Herbert, J. c-fos expression, behavioural, endocrine and autonomic responses to acute social stress in male rats after chronic restraint: modulation by serotonin. *Neuroscience* **95**, 453-63 (2000).
114. Kollack-Walker, S., Don, C., Watson, S.J. & Akil, H. Differential expression of c-fos mRNA within neurocircuits of male hamsters exposed to acute or chronic defeat. *J Neuroendocrinol* **11**, 547-59 (1999).
115. Martinez, M., Phillips, P.J. & Herbert, J. Adaptation in patterns of c-fos expression in the brain associated with exposure to either single or repeated social stress in male rats. *Eur J Neurosci* **10**, 20-33 (1998).
116. Fan, Y. et al. Early life stress modulates amygdala-prefrontal functional connectivity: Implications for oxytocin effects. *Hum Brain Mapp* **35**, 5328-39 (2014).
117. Meyer-Lindenberg, A. et al. Neural mechanisms of genetic risk for impulsivity and violence in humans. *Proc Natl Acad Sci U S A* **103**, 6269-74 (2006).
118. Pezawas, L. et al. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. *Nat Neurosci* **8**, 828-34 (2005).
119. Toth, M. et al. The neural background of hyper-emotional aggression induced by post-weaning social isolation. *Behav Brain Res* **233**, 120-9 (2012).
120. Veit, R. et al. Aberrant social and cerebral responding in a competitive reaction time paradigm in criminal psychopaths. *Neuroimage* **49**, 3365-72 (2010).
121. Tulogdi, A. et al. Brain mechanisms involved in predatory aggression are activated in a laboratory model of violent intra-specific aggression. *Eur J Neurosci* **32**, 1744-53 (2010).
122. Tulogdi, A. & al., e. Neural mechanisms of predatory aggression in rats - implications for abnormal intraspecific aggression. *Behav. Brain Res.* (2014).
123. Vitiello, B., Behar, D., Hunt, J., Stoff, D. & Ricciuti, A. Subtyping aggression in children and adolescents. *J Neuropsychiatry Clin Neurosci* **2**, 189-92 (1990).
124. Kinnally, E.L. et al. Serotonin transporter expression is predicted by early life stress and is associated with disinhibited behavior in infant rhesus macaques. *Genes Brain and Behavior* **9**, 45-52 (2010).
125. Higley, J.D. et al. Cerebrospinal fluid monoamine and adrenal correlates of aggression in free-ranging rhesus monkeys. *Arch Gen Psychiatry* **49**, 436-41 (1992).
126. Cao, J.L. et al. Mesolimbic Dopamine Neurons in the Brain Reward Circuit Mediate Susceptibility to Social Defeat and Antidepressant Action. *Journal of Neuroscience* **30**, 16453-16458 (2010).

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

127. Russo, S.J. & Nestler, E.J. The brain reward circuitry in mood disorders. *Nat Rev Neurosci* **14**, 609-25 (2013).
128. Miczek, K.A., Covington, H.E., 3rd, Nikulina, E.M., Jr. & Hammer, R.P. Aggression and defeat: persistent effects on cocaine self-administration and gene expression in peptidergic and aminergic mesocorticolimbic circuits. *Neurosci Biobehav Rev* **27**, 787-802 (2004).
129. Chaudhury, D. et al. Rapid regulation of depression-related behaviours by control of midbrain dopamine neurons. *Nature* **493**, 532-6 (2013).
130. Francis, T.C. et al. Nucleus Accumbens Medium Spiny Neuron Subtypes Mediate Depression-Related Outcomes to Social Defeat Stress. *Biol Psychiatry* (2014).
131. Trainor, B.C. Stress responses and the mesolimbic dopamine system: social contexts and sex differences. *Horm Behav* **60**, 457-69 (2011).
132. Campi, K.L., Greenberg, G.D., Kapoor, A., Ziegler, T.E. & Trainor, B.C. Sex differences in effects of dopamine D1 receptors on social withdrawal. *Neuropharmacology* **77**, 208-16 (2014).
133. Cabib, S. & Puglisi-Allegra, S. The mesoaccumbens dopamine in coping with stress. *Neurosci Biobehav Rev* **36**, 79-89 (2012).
134. Lucas, L.R. et al. Repeated exposure to social stress has long-term effects on indirect markers of dopaminergic activity in brain regions associated with motivated behavior. *Neuroscience* **124**, 449-57 (2004).
135. Caspi, A. et al. Role of genotype in the cycle of violence in maltreated children. *Science* **297**, 851-4 (2002).

Landmark study showing that early life stress interacts with specific gene polymorphisms (in this case MAOA gene) increaseing the risk to develp violent behaviors.

136. Schwandt, M.L. et al. Gene-environment interactions and response to social intrusion in male and female rhesus macaques. *Biol Psychiatry* **67**, 323-30 (2010).
137. Conway, C.C. et al. Coaction of stress and serotonin transporter genotype in predicting aggression at the transition to adulthood. *J Clin Child Adolesc Psychol* **41**, 53-63 (2012).
138. Verona, E., Joiner, T.E., Johnson, F. & Bender, T.W. Gender specific gene-environment interactions on laboratory-assessed aggression. *Biol Psychol* **71**, 33-41 (2006).
139. Lawford, B.R., Young, R., Noble, E.P., Kann, B. & Ritchie, T. The D-2 dopamine receptor (DRD2) gene is associated with co-morbid depression, anxiety and social dysfunction in untreated veterans with post-traumatic stress disorder. *European Psychiatry* **21**, 180-185 (2006).
140. Zohsel, K. et al. Mothers' prenatal stress and their children's antisocial outcomes - a moderating role for the dopamine receptor D4 (DRD4) gene. *Journal of Child Psychology and Psychiatry* **55**, 69-76 (2014).
141. Buchmann, A.F. et al. Interaction between prenatal stress and dopamine D4 receptor genotype in predicting aggression and cortisol levels in young adults. *Psychopharmacology* **231**, 3089-3097 (2014).
142. Lloyd, R.B. & Nemeroff, C.B. The role of corticotropin-releasing hormone in the pathophysiology of depression: therapeutic implications. *Curr Top Med Chem* **11**, 609-17 (2011).
143. Maestripieri, D., Lindell, S.G., Ayala, A., Gold, P.W. & Higley, J.D. Neurobiological characteristics of rhesus macaque abusive mothers and their relation to social and maternal behavior. *Neurosci Biobehav Rev* **29**, 51-7 (2005).
144. Veenit, V., Riccio, O. & Sandi, C. CRHR1 links peripuberty stress with deficits in social and stress-coping behaviors. *J Psychiatr Res* **53**, 1-7 (2014).
145. Ivy, A.S., Brunson, K.L., Sandman, C. & Baram, T.Z. Dysfunctional nurturing behavior in rat dams with limited access to nesting material: a clinically relevant model for early-life stress. *Neuroscience* **154**, 1132-42 (2008).

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

146. Sandi, C. et al. Chronic stress-induced alterations in amygdala responsiveness and behavior--modulation by trait anxiety and corticotropin-releasing factor systems. *Eur J Neurosci* **28**, 1836-48 (2008).
147. Pournajafi-Nazarloo, H. et al. Stress differentially modulates mRNA expression for corticotrophin-releasing hormone receptors in hypothalamus, hippocampus and pituitary of prairie voles. *Neuropeptides* **43**, 113-23 (2009).
148. Tazi, A. et al. Corticotropin-releasing factor antagonist blocks stress-induced fighting in rats. *Regul Pept* **18**, 37-42 (1987).
149. Cooper, M.A. & Huhman, K.L. Corticotropin-releasing factor receptors in the dorsal raphe nucleus modulate social behavior in Syrian hamsters. *Psychopharmacology (Berl)* **194**, 297-307 (2007).
150. Bosch, O.J., Nair, H.P., Ahern, T.H., Neumann, I.D. & Young, L.J. The CRF system mediates increased passive stress-coping behavior following the loss of a bonded partner in a monogamous rodent. *Neuropsychopharmacology* **34**, 1406-15 (2009).
151. Hostetler, C.M. & Ryabinin, A.E. The CRF system and social behavior: a review. *Front Neurosci* **7**, 92 (2013).
152. Neumann, I.D. & Landgraf, R. Balance of brain oxytocin and vasopressin: implications for anxiety, depression, and social behaviors. *Trends Neurosci* **35**, 649-59 (2012).
153. Meyer-Lindenberg, A., Domes, G., Kirsch, P. & Heinrichs, M. Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. *Nature Reviews Neuroscience* **12**, 524-538 (2011).
154. Cao, Y. et al. Neonatal paternal deprivation impairs social recognition and alters levels of oxytocin and estrogen receptor alpha mRNA expression in the MeA and NAcc, and serum oxytocin in mandarin voles. *Horm Behav* **65**, 57-65 (2014).
155. Lukas, M. et al. The Neuropeptide Oxytocin Facilitates Pro-Social Behavior and Prevents Social Avoidance in Rats and Mice. *Neuropsychopharmacology* **36**, 2159-2168 (2011).
156. Timmer, M., Cordero, M.I., Sevelinges, Y. & Sandi, C. Evidence for a role of oxytocin receptors in the long-term establishment of dominance hierarchies. *Neuropsychopharmacology* **36**, 2349-56 (2011).
157. Cordero, M.I. & Sandi, C. Stress amplifies memory for social hierarchy. *Front Neurosci* **1**, 175-84 (2007).
158. Lukas, M., Toth, I., Veenema, A.H. & Neumann, I.D. Oxytocin mediates rodent social memory within the lateral septum and the medial amygdala depending on the relevance of the social stimulus: male juvenile versus female adult conspecifics. *Psychoneuroendocrinology* **38**, 916-26 (2013).
159. Lee, P.R., Brady, D.L., Shapiro, R.A., Dorsa, D.M. & Koenig, J.I. Prenatal stress generates deficits in rat social behavior: Reversal by oxytocin. *Brain Res* **1156**, 152-67 (2007).
160. Veenema, A.H. Toward understanding how early-life social experiences alter oxytocin- and vasopressin-regulated social behaviors. *Horm Behav* **61**, 304-12 (2012).
161. Lukas, M., Bredewold, R., Landgraf, R., Neumann, I.D. & Veenema, A.H. Early life stress impairs social recognition due to a blunted response of vasopressin release within the septum of adult male rats. *Psychoneuroendocrinology* **36**, 843-53 (2011).
162. Heim, C. et al. Lower CSF oxytocin concentrations in women with a history of childhood abuse. *Molecular Psychiatry* **14**, 954-958 (2009).
163. Bertsch, K., Schmidinger, I., Neumann, I.D. & Herpertz, S.C. Reduced plasma oxytocin levels in female patients with borderline personality disorder. *Horm Behav* **63**, 424-9 (2013).
164. Smearman, E.L., Winiarski, D.A., Brennan, P.A., Najman, J. & Johnson, K.C. Social stress and the oxytocin receptor gene interact to predict antisocial behavior in an at-risk cohort. *Dev Psychopathol*, 1-10 (2014).

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

165. Zovkic, I.B., Meadows, J.P., Kaas, G.A. & Sweatt, J.D. Interindividual Variability in Stress Susceptibility: A Role for Epigenetic Mechanisms in PTSD. *Front Psychiatry* **4**, 60 (2013).
166. Weaver, I.C. et al. Epigenetic programming by maternal behavior. *Nat Neurosci* **7**, 847-54 (2004).
167. Golden, S.A. et al. Epigenetic regulation of RAC1 induces synaptic remodeling in stress disorders and depression. *Nat Med* **19**, 337-44 (2013).
168. Hornung, O.P. & Heim, C.M. Gene-environment interactions and intermediate phenotypes: early trauma and depression. *Front Endocrinol (Lausanne)* **5**, 14 (2014).
169. Sandi, C. Stress and cognition. *Wiley Interdisciplinary Reviews-Cognitive Science* **4**, 245-61 (2013).
170. Pinker, S. The Better Angels of our Nature (New York: Viking 2011).
171. Dang, C.P., Braeken, J., Colom, R., Ferrer, E. & Liu, C. Why is working memory related to intelligence? Different contributions from storage and processing. *Memory* **22**, 426-441 (2014).
172. Vollhardt, J.R. & Staub, E. Inclusive altruism born of suffering: the relationship between adversity and prosocial attitudes and behavior toward disadvantaged outgroups. *Am J Orthopsychiatry* **81**, 307-15 (2011).
173. Schreiter, S., Pijnenborg, G.H.M. & aan het Rot, M. Empathy in adults with clinical or subclinical depressive symptoms. *Journal of Affective Disorders* **150**, 1-16 (2013).
174. Nietlisbach, G., Maercker, A., Rossler, W. & Haker, H. Are empathic abilities impaired in posttraumatic stress disorder? *Psychological Reports* **106**, 832-844 (2010).
175. Mazza, M. et al. Social cognition disorders in military police officers affected by posttraumatic stress disorder after the attack of An-Nasiriyah in Iraq 2006. *Psychiatry Res* **198**, 248-52 (2012).
176. Nazarov, A. et al. Theory of mind performance in women with posttraumatic stress disorder related to childhood abuse. *Acta Psychiatr Scand* **129**, 193-201 (2014).
177. Sapolsky, R.M. The influence of social hierarchy on primate health. *Science* **308**, 648-52 (2005).

Pioneer work linking status in social hierarchy with different physiological outcomes.

178. Bushman, B.J., Wang, M.C. & Anderson, C.A. Is the curve relating temperature to aggression linear or curvilinear? Assaults and temperature in Minneapolis reexamined. *Journal of Personality and Social Psychology* **89**, 62-66 (2005).
179. Freeman, T.W. & Roca, V. Gun use, attitudes toward violence, and aggression among combat veterans with chronic posttraumatic stress disorder. *Journal of Nervous and Mental Disease* **189**, 317-320 (2001).
180. Painuly, N., Sharan, P. & Mattoo, S.K. Relationship of anger and anger attacks with depression: a brief review. *Eur Arch Psychiatry Clin Neurosci* **255**, 215-22 (2005).
181. Painuly, N., Sharan, P. & Mattoo, S.K. Antecedents, concomitants and consequences of anger attacks in depression. *Psychiatry Res* **153**, 39-45 (2007).
182. Bruce, L.C., Heimberg, R.G., Blanco, C., Schneier, F.R. & Liebowitz, M.R. Childhood maltreatment and social anxiety disorder: implications for symptom severity and response to pharmacotherapy. *Depress Anxiety* **29**, 131-8 (2012).
183. Roth, D.A., Coles, M.E. & Heimberg, R.G. The relationship between memories for childhood teasing and anxiety and depression in adulthood. *Journal of Anxiety Disorders* **16**, 149-164 (2002).
184. Storch, E.A., Masia-Warner, C., Crisp, H. & Klein, R.G. Peer victimization and social anxiety in adolescence: A prospective study. *Aggressive Behavior* **31**, 437-452 (2005).

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

185. Merrifield, C., Balk, D. & Moscovitch, D.A. Self-portrayal concerns mediate the relationship between recalled teasing and social anxiety symptoms in adults with anxiety disorders. *J Anxiety Disord* **27**, 456-60 (2013).
186. Kim-Cohen, J. et al. MAOA, maltreatment, and gene-environment interaction predicting children's mental health: new evidence and a meta-analysis. *Mol Psychiatry* **11**, 903-13 (2006).
187. Perepletchikova, F. & Kaufman, J. Emotional and behavioral sequelae of childhood maltreatment. *Curr Opin Pediatr* **22**, 610-5 (2010).
188. Eaves, L.J., Prom, E.C. & Silberg, J.L. The mediating effect of parental neglect on adolescent and young adult anti-sociality: a longitudinal study of twins and their parents. *Behav Genet* **40**, 425-37 (2010).
189. Verona, E. & Sachs-Ericsson, N. The intergenerational transmission of externalizing behaviors in adult participants: the mediating role of childhood abuse. *J Consult Clin Psychol* **73**, 1135-45 (2005).
190. McKinney, C.M., Caetano, R., Ramisetty-Mikler, S. & Nelson, S. Childhood family violence and perpetration and victimization of intimate partner violence: findings from a national population-based study of couples. *Ann Epidemiol* **19**, 25-32 (2009).
191. Staub, E. & Vollhardt, J. Altruism born of suffering: the roots of caring and helping after victimization and other trauma. *Am J Orthopsychiatry* **78**, 267-80 (2008).
192. von Dawans, B., Fischbacher, U., Kirschbaum, C., Fehr, E. & Heinrichs, M. The social dimension of stress reactivity acute stress increases prosocial behavior in humans. *Psychological science* **23**, 651-660 (2012).
193. Vinkers, C.H. et al. Time-dependent changes in altruistic punishment following stress. *Psychoneuroendocrinology* **38**, 1467-75 (2013).
194. Gneezy, A. & Fessler, D.M. Conflict, sticks and carrots: war increases prosocial punishments and rewards. *Proc Biol Sci* **279**, 219-23 (2012).
195. Bauer, M., Cassar, A., Chytilova, J. & Henrich, J. War's enduring effects on the development of egalitarian motivations and in-group biases. *Psychol Sci* **25**, 47-57 (2014).
196. Gutman, D.A. & Nemeroff, C.B. Neurobiology of early life stress: rodent studies. *Semin Clin Neuropsychiatry* **7**, 89-95 (2002).
197. Darnaudery, M. & Maccari, S. Epigenetic programming of the stress response in male and female rats by prenatal restraint stress. *Brain Res Rev* **57**, 571-85 (2008).
198. Ruedi-Bettschen, D. et al. Early deprivation leads to altered behavioural, autonomic and endocrine responses to environmental challenge in adult Fischer rats. *Eur J Neurosci* **24**, 2879-93 (2006).
199. Sandi, C. Stress, cognitive impairment and cell adhesion molecules. *Nat Rev Neurosci* **5**, 917-30 (2004).
200. Kohl, C. et al. The interplay of conditional NCAM-knockout and chronic unpredictable stress leads to increased aggression in mice. *Stress* **16**, 647-54 (2013).
201. Gregg, T.R. & Siegel, A. Brain structures and neurotransmitters regulating aggression in cats: implications for human aggression. *Prog Neuropsychopharmacol Biol Psychiatry* **25**, 91-140 (2001).
202. Sudhof, T.C. Neuroligins and neurexins link synaptic function to cognitive disease. *Nature* **455**, 903-11 (2008).
203. Gogolla, N. et al. Common circuit defect of excitatory-inhibitory balance in mouse models of autism. *J Neurodev Disord* **1**, 172-81 (2009).
204. Yizhar, O. et al. Neocortical excitation/inhibition balance in information processing and social dysfunction. *Nature* **477**, 171-8 (2011).
205. Karst, H. & Joels, M. Effect of chronic stress on synaptic currents in rat hippocampal dentate gyrus neurons. *J Neurophysiol* **89**, 625-33 (2003).

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

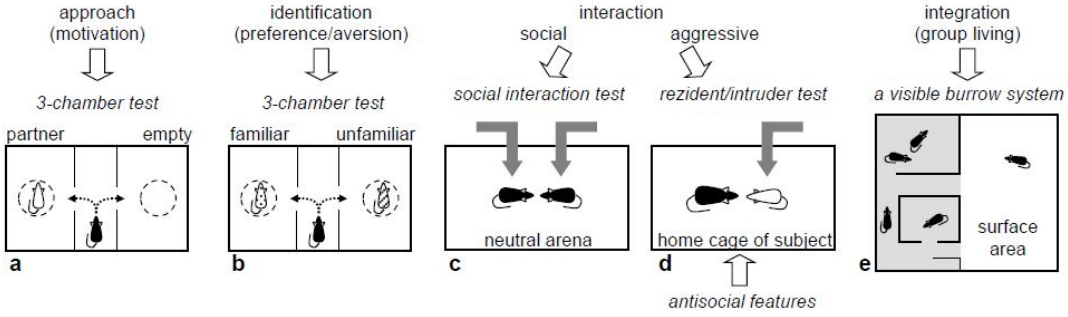
206. Reagan, L.P. et al. Chronic restraint stress up-regulates GLT-1 mRNA and protein expression in the rat hippocampus: reversal by tianeptine. *Proc Natl Acad Sci U S A* **101**, 2179-84 (2004).
207. Hu, W., Zhang, M., Czeh, B., Flugge, G. & Zhang, W. Stress impairs GABAergic network function in the hippocampus by activating nongenomic glucocorticoid receptors and affecting the integrity of the parvalbumin-expressing neuronal network. *Neuropsychopharmacology* **35**, 1693-707 (2010).
208. Kohl, C. et al. Hippocampal neuroligin-2 overexpression leads to reduced aggression and inhibited novelty reactivity in rats. *PLoS ONE* **8**, e56871 (2013).
209. Ditzen, B. & Heinrichs, M. Psychobiology of social support: the social dimension of stress buffering. *Restor Neurol Neurosci* **32**, 149-62 (2014).
210. Windle, R.J., Shanks, N., Lightman, S.L. & Ingram, C.D. Central oxytocin administration reduces stress-induced corticosterone release and anxiety behavior in rats. *Endocrinology* **138**, 2829-34 (1997).
211. Waldherr, M. & Neumann, I.D. Centrally released oxytocin mediates mating-induced anxiolysis in male rats. *Proc Natl Acad Sci U S A* **104**, 16681-4 (2007).
212. Smith, A.S. & Wang, Z. Hypothalamic oxytocin mediates social buffering of the stress response. *Biol Psychiatry* **76**, 281-8 (2014).
213. Berardi, A. et al. An updated animal model capturing both the cognitive and emotional features of post-traumatic stress disorder (PTSD). *Front Behav Neurosci* **8**, 142 (2014).
214. Daskalakis, N.P. et al. Early experience of a novel-environment in isolation primes a fearful phenotype characterized by persistent amygdala activation. *Psychoneuroendocrinology* **39**, 39-57 (2014).

Interesting study showing that social buffering of stress is not only reflected in immediate effects but can have long-term consequences when it occurs during early life.

215. Stamatakis, A., Diamantopoulou, A., Panagiotaropoulos, T., Raftogianni, A. & Stylianopoulou, F. Effects of an Early Experience Involving Training in a T-Maze Under either Denial or Receipt of Expected Reward through Maternal Contact. *Front Endocrinol (Lausanne)* **4**, 178 (2013).
216. Rincon-Cortes, M. & Sullivan, R.M. Early life trauma and attachment: immediate and enduring effects on neurobehavioral and stress axis development. *Front Endocrinol (Lausanne)* **5**, 33 (2014).
217. Sarro, E.C., Wilson, D.A. & Sullivan, R.M. Maternal Regulation of Infant Brain State. *Current Biology* **24**, 1664-1669 (2014).

You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

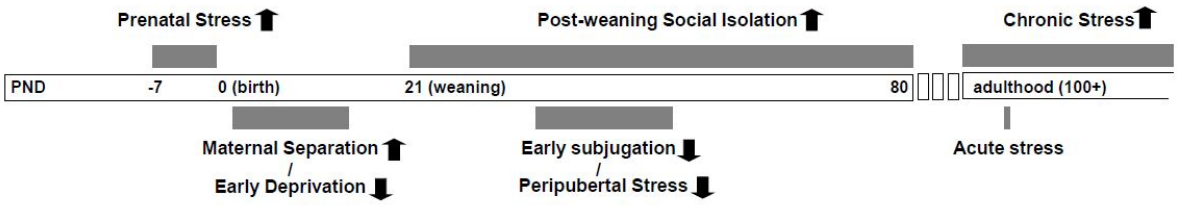
Figure - Box 2



You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

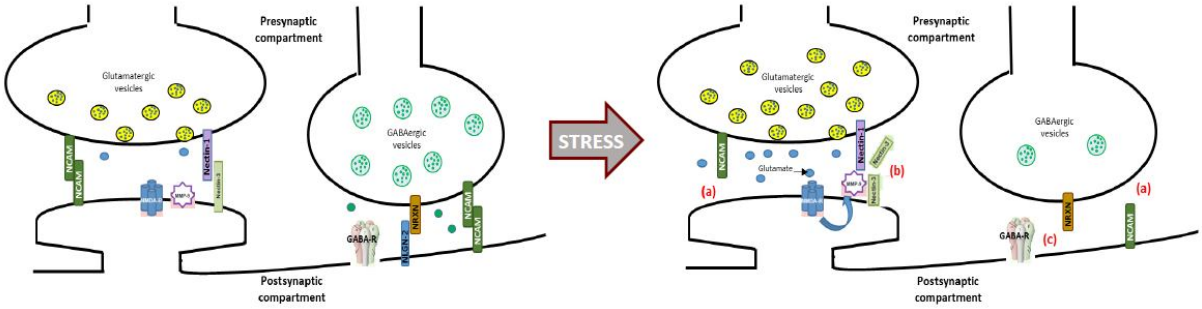
Figure Box 3

The programming of glucocorticoid responsiveness by different stress models



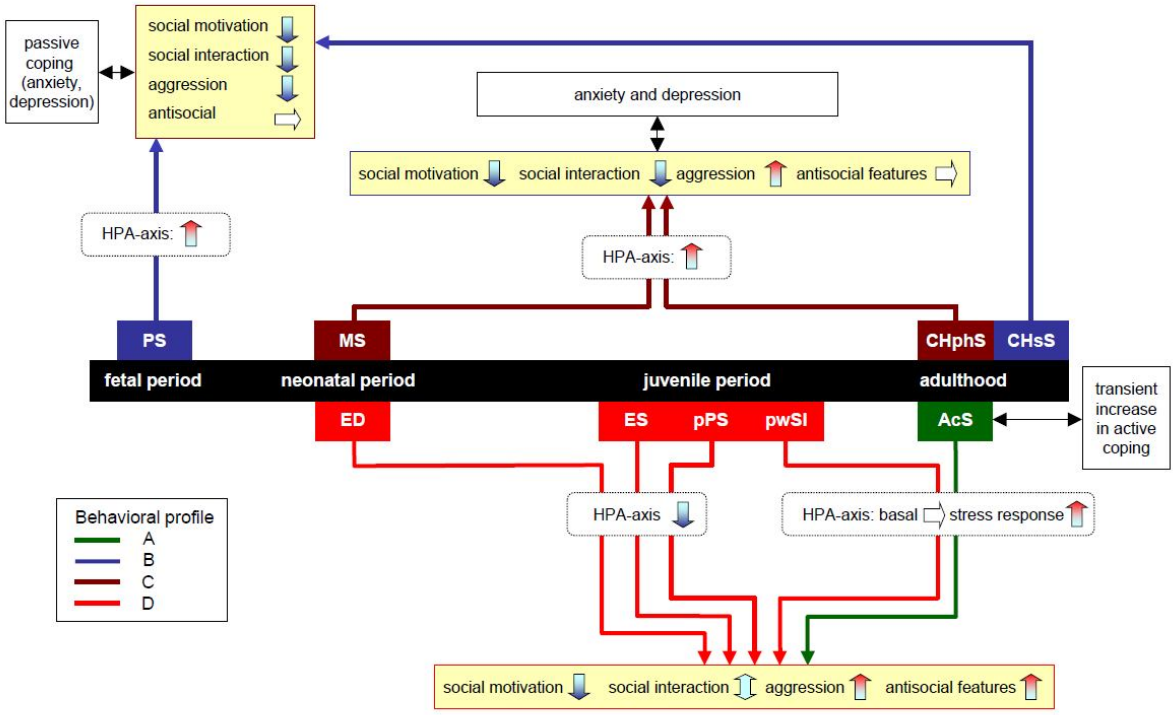
You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

Figure Box 4



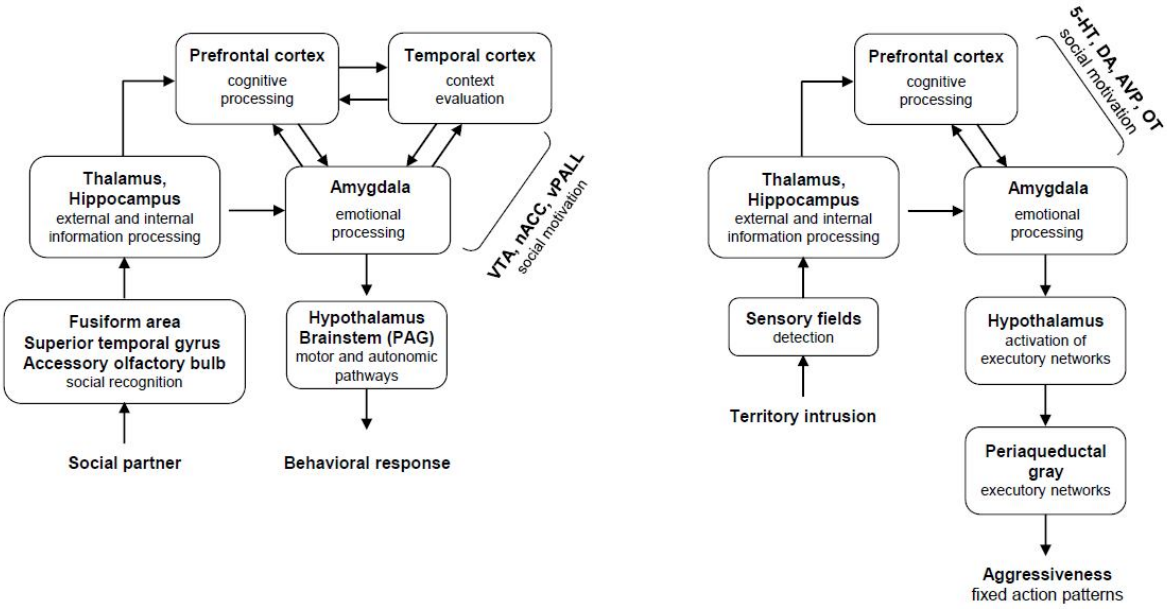
You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

Figure 1



You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)

Figure 2



You created this PDF from an application that is not licensed to print to novaPDF printer (http://www.novapdf.com)