Biobehavioural background of a stress and the social stressor relation to Cognitive Function

Abstract
Stress more often affects our social lives. Undergoing high level or persistent stress, implicate that individuals frequently retract from social interactions and provide to be irritable and hostile. Moreover it provides to impairment of cognitive function. Exposure to stress modulated by early-life adversity could provide to cognitive function impairment; moreover, the effects of early-life stress depend on the timing of exposure and genetic factors. Executive function (EF) is an umbrella term that refers to processes that control other cognitive processes. Nevertheless, there is ample evidence that prolonged stress provides alterations in brain structure tied to cognitive function.

Keywords: stress; social stressor; cognitive function.
A stress response is an evolutionary heritage of ability to anticipate, identify and effectively respond to danger. After millions of years of evolution, perception of variety of stressors mobilizes neurologic, neuroendocrine, endocrine, immunologic and metabolic systems to maintain an ability to survive and propagate gens (natural selection). Additionally, in humans these mechanisms involve complex and interrelated mental, emotional, behavioural and social processes. Behavioural adaptation is aimed on modulation of neural pathways that help to cope with stressful situations. These e.g. include changes of sensory thresholds, increased alertness, memory enhancement, suppression of hunger, and stress-induced analgesia.

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 (Kloet & Holsboer, 2005). However, sustained stress can have strong and long-lasting adverse effects on brain function and behaviour. (Lupien, McEwen, Gunnar & Heim, 2009).

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 recognised a century ago, 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 behaviour that seem to be linked to stress—from income inequalities and economic crises (indirect indexes of stress) that uphold societal-level violence to severe stressors that induce marked dysfunctions in individuals’ social functioning (Kennedy & Adolphs, 2012).

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 behaviour. 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 behaviour 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 analyses 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 behaviour. 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 behavior Conceptualisations of stress usually emphasise the following elements: a state of arousal resulting either from the presence of socioenvironmental demands that tax the ordinary adaptive capacity of the individual or from the absence of the means to attain sought-after ends (Pearlin 1983, Menaghan 1983). External circumstances that challenge or obstruct are labeled stressors; Stress refers to internal arousal. Thus, stress is not an inherent attribute of external conditions, but emanates from discrepancies between those conditions and characteristics of the individual his or her needs, values, perceptions, resources, and skills. In an analogy to engineering physics, Smith (1987) maintained that stress should be assessed not merely as load, but as load relative to the supporting surface.

Socioenvironmental conditions differ in the capacity to evoke stress, however; some conditions threaten virtually everyone, whereas others are uniformly navigated with ease. This principle is illustrated by the various strategies developed to weight life events according to the average amount of readjustment required (e.g. Dohrenwend et al 1978). Events differ from one another in average ratings, due to characteristics of the event, and ratings of a single event differ across raters, due to characteristics of the rater. The presence of both inter-event and intra-event variation mirrors the interplay of person and environment.

Stress research continues to emphasize one particular type of stressor, life-event change. This emphasis has persisted despite long-standing, cogent criticism that enduring problems of ordinary social life have been neglected. B.S.Dohrenwend(1978) defined life-event stressors as objective occurrences of sufficient magnitude to change the usual activities of most persons. The initial conceptualization of any change as stress-provoking has given way to agreement that undesirable events are most psychologically distressing; other dimensions such as whether events can be controlled or predicted are of secondary importance (Ross & Mirowsky 1979). The deleterious health effects of life change are of consistently modest magnitude; few who encounter life events suffer ill health as a result. Kessler and associates (1985) described several strategies used to address an assumed problem of measurement-error attenuation: specifying especially stress-provoking events, assessing duration and recency of exposure, and specifying context. Improved measures, however, have not increased noticeably the association between events and psychological distress (Thoits 1983). Consequently, attention has shifted to social psychological factors regulating the impact of stress (Kessler et al 1985). Most prominent is the concept of social support. Definitions of support abound, but most include whether a person’s basic social needs—affection, esteem, approval, belonging, identity and security—are satisfied through interaction with others (Thoits 1983). Three distinct dimensions: integration, the existence of relations;_networks, their structure; and support systems, their so-
cioemotional, instrumental, informational, and appraisal dimensions. Social support, especially socioemotional support, is related inversely to diverse forms of psychological disorder, physical morbidity, and mortality (e.g. Turner 1981, Ross & Mirowsky 1989). Longitudinal studies demonstrate reciprocal relationships: causal influence goes from support to mental health and vice versa (Turner 1981). A major emphasis concerns whether social support acts as a stress-buffer, ameliorating the deleterious effects of stress. In reviewing this contradictory literature, Kessler & McLeod (1985) concluded that the mental health impact of stress is buffered by emotional and perceived social support, but not by membership in social networks.

Research concerning the nature and effectiveness of coping also has proliferated over the past decade. Folkman & Lazarus (1980) defined coping as cognitive and behavioural efforts made to master, tolerate, or reduce external and internal demands and conflicts. Coping behavior differs from coping resources, that is, from preexisting assets such as self-esteem called upon when stress does arise. Functions of coping include avoiding or eliminating the stressor, containing the proliferation of secondary stressors, altering the meaning of the situation, and managing states of arousal (Pearlin & Schooler 1978). Folkman & Lazarus (1980) categorized coping as problem-focused versus emotion-focused. Coping and social support are functionally isomorphic concepts. For example, Thoits (1984) conceptualized social support as coping assistance. Coping refers to actions taken in one’s own behalf, whereas support refers to actions undertaken by another person. Coping and social support perform parallel functions, influencing the occurrence and impact of stressful life experiences (Pearlin & Aneshensel 1986).

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 behaviors such as bite counts that exceed species-typical levels. This fits with the concept of acute stress as a ‘flight or fight’ response and implies that brief acute stressors mobilize resources to cope with the situation (Takahashi, et al. 2012).

Chronic stress (the stressor is recurrent or is sustained over several days) reduces social motivation and social interactions in a variety of sociability tests, particularly in highly anxious animals. For example, chronic social defeat induces social avoidance and social fear towards unknown conspecifics, 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, probably because long-term deprivation from social contacts 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 permeate interactions in the monogamous, biparental California
mouse (Peromyscus californicus) male subjected to chronic variable stress (Harris, de Jong, Yang & Saltzman, 2013).

Aggressiveness is increased by chronic physical stressors — including chronic unpredictable mild stress, restraint or immobilization— in mice and rats, as well as by social stressors such as social isolation in rodents and social and spatial restrictions in dogs. Interestingly, chronic immobilization escalated both normative aggressive behaviour (attacking small adversaries with a high chance of winning) and ‘risky’ aggression (attacking big adversaries, with a low chance of winning) in rats. 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. 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 (Beerda, et. al., 1999; Nephew & Bridges, 2011).

STRESS DURING DEVELOPMENT

Stress models that cover a range of neuroontogenesis periods have been applied to investigate the long-term impact of stress on adult social behaviours. Social motivation (sociability) was disrupted in adulthood by prenatal; neonatal and juvenile exposure to stressors. By contrast, the execution of social behaviours in the social interaction test was affected differentially by stressors administered at different ages. Prenatal stress, neonatal stressors (maternal separation) and early deprivation (and peripubertal exposure to physical stressors ) inhibited social interactions in adulthood. Interestingly, early social deprivation also inhibited pair bonding in mandarin voles. Juvenile social stressors (post-weaning social isolation and early subjugation either did not affect this aspect of social behaviour or, in one study, increased adult social interactions (de Souza at al., 2013).

The effects of early stressors on adult behaviour in the resident–intruder test are even more variable. Here, prenatal stress reduced aggressiveness. Maternal separation, by contrast, increased inter-male aggressiveness in rats (but not mice, although female mice showed increased maternal aggression. Specifically, the latency of attack was reduced and/or the duration of offensive threats was increased, although bite counts remained unchanged. Early deprivation increased all three components of aggression and stressors administered to juveniles also enhanced aggressiveness in adulthood (Veenema, Bredewold & Neumann, 2007).

Importantly, antisocial features of aggression were found to emerge mainly when animals were stressed at juvenile ages. All symptoms of ‘antisociality’ were observed in both the post-weaning social isolation and peripubertal non-social stress models. 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 behavioural 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. 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. Interestingly, antisocial features of aggression, particularly offensive ambiguity, 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 behaviours, increase aggressiveness, and promote the development of antisocial features, but the specific consequences depend on the timing and type of the early stressor. 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. For example, enhanced 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 behaviour (Provencal & Binder, 2014).

**INTERGENERATIONAL EFFECTS**

Animal studies have shown that the effects of stress on social behaviours 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. In rats, both the female and male behaviour offspring of dams exposed to chronic stress during lactation displayed decreased social behaviour as juveniles and adults. Similarly, the offspring of prepubertal stressed male rats that had had no direct interactions with their father showed increased aggression. Several mechanisms may drive these transgenerational effects, including changes in the females (such as altered maternal behaviour and/or physiological changes) that mated with the stressed male and epigenetic processes transmitted through the germline (Gapp, et al., 2014).

**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 through mineralocorticoid receptors (MR) and glucocorticoid receptors (GR); which mediate their effects through both genomic (slow) and non-genomic (rapid) mechanisms. In addition to mediate effects of the activation
of these receptors, glucocorticoids can also exert long lasting programming effects on brain function and behaviour (de Kloet, Karst & Joels, 2008).

**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) 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. These changes in glucocorticoid levels seem to contribute to many of the changes in social behaviours induced by stressors. Three of the rodent developmental stress models resulting in antisocial aggression discussed above — early deprivation, early subjugation and prepubertal stress — are characterised by long-term decreases in HPA-axis activity. A fourth model — post-weaning social isolation — is characterised by normal basal HPA-axis activity, but enhanced autonomic and glucocorticoid responses to stress, which may drive the increased-stress induced aggression seen in adults in this model.

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) and in the neural circuitry — including the pre optic area and other hypothalamic nuclei projecting to the periventricular nucleus — that regulates the activity of hypothalamic neurons expressing corticotropin releasing hormone (CRH) (Rees, Steiner & Fleming, 2006).

**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 stress on social behaviour. These treatments induced effects on social behaviours that were highly consistent with those seen in stress models. Corticosterone treatment in neonates mimicked the diminished adult social exploration and increased submissiveness observed in maternally deprived mice. Corticosterone treatment in juvenile rats diminished social exploration as did exposure to prepuberty stress and acute glucocorticoid treatments in adulthood increased aggressive behaviour as did acute stress elicited by frustration (Blair, 2007).
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 behaviour and increased aggression. In another example, mimicking the reduction in HPA axis activity in adulthood caused by early deprivation, early subjugation and non-social prepubertal stressors (through adrenalectomy with low-level glucocorticoid replacement) led to decreased social behaviours and anti-sociality. This was abolished by repeated glucocorticoid treatments suggesting that the long-term suppression of HPA-axis function and the altered social behaviour in these models are causally related. Therefore, both excesses and deficits in glucocorticoid production have detrimental effects on social behaviour (Tzanoulinou, et al. 2014; Haller & Kruk, 2006).

These findings indicate that glucocorticoid signalling at least partly mediates the behavioural 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 sub-chronic social defeat procedure in mice. Moreover, in humans, an interaction between genetic variation in the gene encoding FKBP5 (a co-chaperone of heat shock protein that affects the transcriptional capacity of GRs) and childhood trauma influences both lifetime history of aggressive behaviour and the glucocorticoid response to stress. These findings suggest that individual differences in the neurodevelopmental trajectories leading to antisocially might be related to genetic neurodevelopment in HPA-axis-related genes that affect the functioning of the stress systems during development and its consequent promotion of long-lasting epigenetic adaptations (Bevilacqua, 2012; Klengel, et al., 2013).

**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 behaviours (hypothalamus, and brainstem motor and autonomic pathways) (Insel & Fernald, 2004). Studies in animals have revealed a ‘social brain network’ that largely overlaps with the human social brain (Kas, Modi, Saxe, & Smith, 2014). In addition, a key role for the periaqueductal gray (PAG) in aggression in animals has been identified and recently confirmed in humans studies (Yu, Mobbs, Seymour, Rowe & Calder, 2014; White, Brislin, Sinclair & Blair, 2014). 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 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 behaviours (Glenn & Raine, 2014; Bruhl, et al., 2014).

Inappropriate social behaviour 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). Although brain development, social learning and remodelling 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 behaviour changes across the lifespan. Prenatal and very early postnatal stress particularly impinge on brain development, whereas stress during childhood and adolescence can also affect social learning. Chronic stressors in adulthood probably exert their effects by remodelling brain circuits that are involved in social behaviour, 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 behaviours.

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 and rodents. Rodent studies suggest an important role for glucocorticoid-induced apoptosis in some of these effects. Structural changes in the same brain areas were observed when chronic stressors were administered to adult rodents. Stress at other developmental stages also causes structural alterations. For instance, neonatal stress affected dendritic organisation and synaptic plasticity in the PFC in rats. Post-weaning social isolation specifically reduced the volume of posterodorsal component of the medial amygdala and of the right medial PFC in rats. However, neural plasticity markers, neurone numbers and basal metabolic activities were not altered in the limbic brain after early social subjugation in rats and hamsters, suggesting that structural changes are minimal following this stressor. Interestingly, early deprivation increased neurone numbers and decreased apoptosis throughout the hypothalamus, whereas it had mixed effects in different hippocampal fields. Taking into consideration the important role of the hypothalamus in aggression control, this suggests that adult consequences of early stressors may be attributed to both structural brain deficits and structural “gains” (Buss, Davis, Muftuler, Head & Sandman, 2010; Desbonnet, Garrett, Daly, McDermott & Dinan, 2008).
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). 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, consistent with the general impairment in social behaviours induced by such stressors (Martinez, Phillips & Herbert, 1998).

Experiencing stress chronically in adulthood or early in life results in alterations in cortico-limbic networks, including changes in amygdala-PFC connectivity. Such changes are also frequently found in individuals with abnormal social behaviours. In most such individuals frontal regions show reduced functioning. However, amygdala activation by emotional stimuli differs between subgroups of antisocial individuals: it shows hypo-functionality in individuals with psychopathic traits and hyper-reactivity in those showing impulsive and reactive social problems. 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. Interestingly, prepubertal 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. Furthermore, alterations in the functional connectivity between the medial orbitofrontal cortex and the amygdala predicted the aggressive behaviour of these mice. However, animals exposed to post-weaning social isolation showed, as adults, activation of both the amygdala and orbitofrontal cortex in response to an intruder. This pattern may mimic findings in criminal psychopathic individuals, who showed enhanced PFC activation when punishing opponents in a competitive game (Veit, et al., 2010).

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), 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 behavioural and emotional features — is often termed ‘predatory’ aggression, especially in the case of psychopathy (Vitiello, Behar, Hunt, Stoff & Ricciuti, 1990).
NEUROCHEMICAL MECHANISMS

Several neurotransmitter and neuropeptide systems were implicated in the effects of stress on social behaviours by neurobiological and pharmacological studies that found correlations between neurotransmitter or neuropeptide expression and effects of stress on social behaviour 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 behaviours. 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 and inversely correlated with cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA; a metabolite of 5-HT) concentrations in adults. In rats exposed to prepubertal 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. Importantly, administration of a MAOA inhibitor in adulthood reversed the deficits in sociability and increased aggression in these rats (Márquez, et al., 2013). Likewise, treatment with the serotonin reuptake inhibitor fluoxetine normalised changes in behaviour, biochemistry and cell firing in mice that were susceptible to the development of social aversion following social defeat stress. Interestingly, changes in the serotonergic system have also been detected in transgenerational studies of stress-induced social deficits. 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 (Cao et al., 2010; Russo & Nestler, 2013).

Studies of social defeat in mice have suggested an involvement of the mesocorticolimbic dopaminergic system. Social defeat leads to reduced social exploration (social avoidance) and a reduced probability of winning future social contests. Social avoidance in such mice was associated with brain-derived neurotrophic factor (BDNF)-induced activation of the receptor tyrosine kinase TRKB signalling pathway in the nucleus accumbens (NAc) and the activation of GRs in neurones expressing dopamine receptors. Upregulation of phasic firing of dopamine neurones that project from the ventral tegmental area (VTA) to the NAc and decreased excitatory synaptic input to dopamine receptor D1-containing medium
spiny neurones from the NAc 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 and individual variation in VTA stress responses has been linked to individual differences in responses to stress. 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. 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. Accordingly, stress-related social subordination in rats has been associated with decreased dopamine transporter binding and increased D2 receptor binding (Lucas, et al. 2014).

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. Subsequently, polymorphisms in the 5-HTT gene were shown to contribute to individual differences in aggressiveness in individuals exposed to stress in early life, at the transition into adulthood or acutely in adulthood. Genetic variants in dopamine 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. Gene variants of the D4 receptor (DRD4), when combined with prenatal maternal stress, were associated with increased antisocial behaviour in childhood and increased aggression and low cortisol responses to social stress at adulthood (Buchmann, et al., 2014).

**EXTRAHYPOTHALAMIC CORTICOTROPIN RELEASING HORMONE (CRH)**

Changes in the expression of components of the extrahypothalamic CRH system following stress and in the context of antisocial behaviours in humans and animals have been shown. They occur, for example, in patients with stress-related psychiatric disorders in which social behaviours are commonly compromised, such as anxiety and depression. Abusive rhesus macaque mothers (who were abused themselves as infants) show higher CSF concentrations of CRH than controls and these are associated with antisocial behaviour patterns. 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. Changes in the extrahypothalamic CRH system have also been observed after stress exposure in other developmental periods in rats and prairie voles, but their role in the associated changes in social behaviour has not been explored. Interestingly, antagonising brain CRH receptors reduced acute stress-induced fighting in rats, decreased the expression of social defeat-induced submissive behaviour in hamsters and reversed passive stress coping behaviour observed in male prairie voles separated from their female partners. Overall, the highly stress-sensitive CRH system seems to play a central role in the regulation of a broad array of social behaviours (Cooper & Huhman, 2007; Hostetler & Rabinin, 2013).

**OXYTOCIN AND VASOPRESSIN**

The neuropeptides arginine vasopressin and oxytocin, which are synthesised in the hypothalamus and limbic system modulating emotional behaviours (such as anxiety and depression), and multiple aspects of social behaviour. Generally, evidence points to a role for vasopressin in promoting antisocial behaviours (such as aggression), whereas oxytocin facilitates prosocial actions (such as social affiliation, attachment, social support, maternal behaviour and trust). Importantly, vasopressin tends to exert anxiogenic effects, whereas oxytocin exerts anxiolytic effects and this difference probably contributes to the contrasting social actions of these neuropeptides (Neumann & Landgraf, 2012; Meyer-Lindenberg, Domes, Kirsch & Heinrichs, 2011).

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 (Neumann & Landgraf, 2012).

Furthermore, in mandarin voles paternal deprivation leading to impaired social recognition, was associated with a reduction in oxytocin receptors in the medial amygdala and nucleus accumbens (Cao et al., 2014).

Whether these modifications have a role in stress-related changes in social behaviours 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. In another study, a reduction in oxytocin receptor expression in the medial amygdala 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 (Cordero & Sandi, 2007). 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, 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 (Lukas, Toth, Veenema & Neumann, 2013).
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. Furthermore, enduring changes in the expression of oxytocin and vasopressin have been observed in adult rodents that had experienced maternal separation stress. 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. In maternally separated female rats, a decrease in hypothalamic oxytocin immunoreactivity was found in the context of increased maternal aggression (Lukas, Bredewold, Landgraf, Neumann & Veenema, 2011).

Lower oxytocin concentrations have also been observed in the CSF and plasma 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 behaviour, when it interacts with developmental stress it is associated with increased levels of antisocial behaviours (Smearman, Winiarski, Brennan, Najman & Johnson, 2014).

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 behaviour, including gene-environment interactions at different developmental periods (Provencal & Binder, 2014; Zovkic, Meadows, Kaas & Sweatt, 2013). 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 behaviour 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 behaviour in rats, 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. Although the precise link with social behaviours 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. 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 behaviours at adulthood in rats. Finally, a role for epigenetic mechanisms has also been suggested for the transmission of some behavioural stress effects across generations. Future studies should more closely define the role of epigenetic modifications in the link between stress and the social brain (Golden, et al. 2013).
CONCLUSIONS

Chance adversity intrudes on the lives of most persons, but stress also arises as a predictable outcome of ordinary social organisation. 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. 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 behaviour. From a developmental perspective, stress appears to impose a progressive pattern of dysfunctional social behaviour that begins with a sociality (elicited by prenatal stressors) progresses to hostility (which emerges when stress is suffered postnatally) and ends with antisocially (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 behaviours. Strikingly, both a sociality 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 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. Stress has demonstrated adverse effects upon psychological and physical health, but these outcomes capture only part of the cost associated with social stress. When discrete health outcomes are investigated, many of those damaged by stress are counted as undamaged because they manifest stress reactions as other outcomes. The total social, psychological, and economic costs of stress have not yet been assessed, therefore, because only some manifestations have been counted. These costs may well include outcomes of relevance to areas of sociological interest other than medical sociology, including crime and delinquency, diminished educational and occupational achievement, lost productivity, and downward social mobility.


