Review

The stress-coping (mis)match hypothesis for nature × nurture interactions

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ABSTRACT

There is high consensus that stress-related disorders like depression are shaped by nature × nurture interactions. However, the complexity appears larger than envisaged and nature × nurture research is progressing too slowly. An important reason is that mainstream research is focussing on the idea that a combination of genotypic stress-sensitivity and stress exposure inevitably leads to maladaptive stress-coping responses, and thereby stress-related disorders. However, stress-coping responses can also be adaptive and adhere to the expected norm. Here I elaborate the 'environment' mismatch hypothesis proposed by Mathias Schmidt (*Psychoneuroendocrinology*, 36, 330–338, 2011) to the stress-coping (mis)match (SCM) hypothesis postulating that stress-coping responses—as programmed by nature × age-dependent nurture interactions—are adaptive when they match current stress conditions, but maladaptive when they mismatch current stress conditions. For instance, acquisition of an active stress-coping response during nurture may lead to the programmed release of active coping responses in current life. This is adaptive when current stress is escapable, but maladaptive when current stress is inescapable, leading to agitation. A model par example for nature × nurture interactions is the serotonin transporter promoter polymorphism, which will be discussed in the framework of the SCM hypothesis. The potential role of the prefrontal–amygdala circuit and the therapeutic implications of the SCM hypothesis will also be discussed.

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1.   The stress-coping (mis)match hypothesis

The longstanding debate in psychiatry on nature or nurture has been reconciled by assuming that both factors contribute to psychopathology. Nature×nurture interactions have indeed been well recognized, particularly in stress-related disorders like depression. Particularly important in nature×nurture research is uncovering the mechanisms whereby nature (genes) influence disease risk as a function of nurture (environmental stimuli). However, research has led to contradictory data and the complexity of nature×nurture interactions appears larger than envisaged. This hampers the understanding of individual differences in vulnerability to stress-related disorders and their treatment.

A major reason for disappointing outcomes of nature×nurture research is that mainstream research is governed by the Diathesis-Stress/Dual Risk hypothesis (Burmeister et al., 2008; Sameroff and Seifer, 1983) that some individuals, because of a genetic "vulnerability", are disproportionately or even exclusively likely to be affected adversely by an environmental stressor. However, it is unlikely that these genes are maintained throughout evolution when they exert outright negative effects. Accordingly, the 'for-better-and-for-worse' (Belsky et al., 2009) concept was introduced, which is based on the idea that 'stress-sensitive' genes actually are 'plasticity' genes. These plasticity genes turn out maladaptive in impoverished, aversive environments, and adaptive in favourable environments. In other words, genes are neither inherently good or bad, but individuals vary in their plasticity or susceptibility to environmental influences. The very same individuals who may be most adversely affected by many kinds of stressors (as postulated by the Diathesis-Stress/Dual Risk hypothesis) may simultaneously benefit the most from environmental support and enrichment. As reviewed by (Homberg and Lesch, 2010), stress in early life increases risk for depression, but only in individuals carrying the short (s) allelic variant of the serotonin transporter-linked polymorphic region (5-HTTLPR, see also Section 3). Yet, s-allele carriers also benefit most of social support and show several types of cognitive improvements in tasks employing rewarding stimuli. These 'for-better-and-for-worse' behavioural manifestations are not limited to the 5-HTTLPR, but are also seen in association with several other common polymorphisms, like the MAOA (monoamine oxidase A) and the DRD4 (dopamine D4 receptor) polymorphisms (Belsky et al., 2009). Despite that the 'for-better-and-for-worse' concept resolves many contradictory nature×nurture findings, it still does not explain why, for instance, depression can also develop under favourable environmental conditions. An important reason is that it is poorly defined what a(n) 'favourable' and 'aversive' environment is.

(Ellis et al., 2011) proposed the "biological sensitivity to context" hypothesis arguing that individuals vary in their susceptibility to environmental influences in much the same way as the "for-better-and-for-worse" concept for nature×nurture

interactions, with the difference that they do not presume that this environment-driven variability is mediated by genotype. Rather, it is their view that experience can shape plasticity, and that a 'fit' between the person and his/her environment determines 'for-better-and-for-worse' outcomes. This evolutionary grounded view relates to the 'environmental mismatch' hypothesis recently proposed by Mathias Schmidt (2011), postulating that depression might be promoted by a mismatch of the programmed and the later actual environment in combination with a more vulnerable or resilient genetic predisposition. Because our 'environmental fit' has much to do with how we cope with environmental challenges I would like to 'merge' these hypotheses and introduce the 'stress-coping (mis)match (SCM)' hypothesis, which postulates that stress-coping responses—as programmed by nature×nurture interactions—are adaptive when they match current stress conditions, but maladaptive when they mismatch (Fig. 1).

The SCM hypothesis is explained as follows. During nurture we learn to cope with stress *actively* (problem-solving, fight/flight) when exposed to *escapable* stress, or *passively* (reduction of harm during stress, quiescence, immobility) when exposed to *inescapable* stress (Bandler et al., 2000). Inescapable or escapable stress experiences during nurture allow stress-sensitive individuals to quickly release conditioned passive or active coping responses, respectively, when re-exposed to stress in current life. These responses will be adaptive when 'nurture' and 'current' stress conditions *match*, for instance when both involve inescapable stress. However, when subjects acquired an active stress-coping response due to exposure to escapable stress condition during nurture and are currently exposed to inescapable stress conditions, which reflect a *mismatch*, they may maladaptively release an active conditioned stress-coping response whereas a passive response is required. In other words, after a successful (i.e. stress reducing) coping response we have the strong tendency to 'get used' to this way of responding. This is very efficient when circumstances in later life are the same, but will work out negatively when circumstances have changed. These adaptive (during matching) and maladaptive (during mismatching) stress-coping responses are likely to be most intense in individuals that are stress-sensitive by genotype, as they get used to successful stress-coping responses more easily. Hence, stress exposure does not inevitably lead to psychopathology in stress-sensitive subjects—as predicted by the Diathesis-Stress/Dual Risk hypothesis—but only when there are environmental mismatches. In terms of the 'for-better-and-for-worse' concept, 'favourable' and 'aversive' environments can then be defined as environments that match and mismatch, respectively, programmed stress-coping responses.

Intuitively, active stress-coping reduces stress, whereas passive stress-coping increases stress. A facilitation of a passive stress-coping response following inescapable stress experiences during nurture is generally considered as a more intense stress response. However, when a passive stress-coping response is considered as a cognitive approach to put the impact of current stress into perspective, for instance by
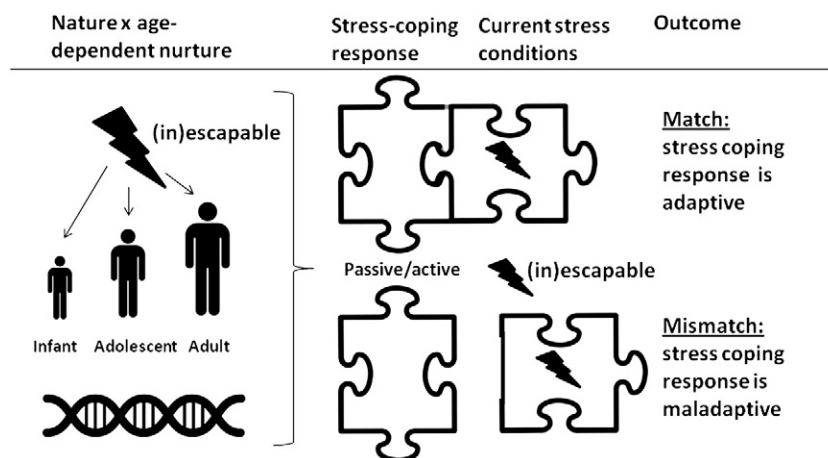
Fig. 1 – The SCM hypothesis: Stress-coping responses are shaped by nature (genotype) and the age (developmental stage) of stress experiences during nurture. When the acquired stress-coping response matches current stress conditions, the response will be adaptive, but mismatching will lead to maladaptive responses and eventually stress-related disorders. The specific nature of the (mis)matches between acquired stress-coping responses and current stress conditions is illustrated in Fig. 2.

thinking "there are worse things that can happen", such a facilitation can actually be very effective to reduce the impact of inescapable stress. Obviously, these kinds of thoughts render subjects helpless when stress is escapable. Also obvious is that an acquired active stress-coping response will allow a faster active stress-coping response upon re-exposure to escapable stress conditions. Yet, an active stress-coping response when stress conditions are inescapable is counterproductive. It leads to the waste of energy and can lead to frustrations, agitation and irritability when actively attempting to reduce the stress if there are no other possibilities than to accept the situation. Thus, active and passive stress-coping do not differ in efficacy to reduce stress. They are dissociated by the inhibition or activation of psychomotor responses to stress.

It is important to note that active and passive stress-coping responses are related, but dissimilar to proactive and reactive coping styles. Proactive coping is defined as an anticipatory, goal-directed act to prevent the effects of stress, which can be active coping, but can also be noted as the inhibition of behaviour (Maier and Watkins, 2010). Reactive coping refers to the reaction to aversive events and harm reduction when the events have occurred. Whereas proactive stress-coping is based on previous experiences, foresight, and predictability of the occurrence of future events, in the context of nature×nurture interactions events cannot always be predicted. That is, the larger the time lag between nurture and current life, the more likely that environmental conditions have changed, and thus have become unpredictable. To address stress-coping in a nature×nurture framework, I therefore focus on active *versus* passive stress-coping for stressful events that have occurred, rather than the proactive/reactive dimension of stress-coping styles. Active/passive stress-coping responses also can be acute or conditioned, which are subserved by different brain mechanisms (Roozendaal et al., 1997). In the context of the SCM hypothesis I only address conditioned stress-coping responses.

In the next sections I will discuss the SCM hypothesis in more detail and present data derived from rodent research

that are in line with the SCM hypothesis. Considering the human serotonin transporter (5-HTT) promoter-linked polymorphic region (5-HTTLPR) as a model par example for nature×nurture interactions, 5-HTTLPR, as well as rodent 5-HTT knockout, findings are used to present new views on existing data. As a mechanistic account I further address the prefrontal cortex–amygdala circuit, which will also be discussed in the framework of developmental changes in the communication between these two areas. Finally, the potential implications of the SCM hypothesis for therapeutic approaches are briefly considered.

2.   Lessons from rodent studies

The basis for the SCM hypothesis is derived from rodent learned helplessness and fear-conditioning studies. In the learned helplessness paradigm animals are pre-exposed ('nurture') to inescapable footshock stress (acquisition of a passive stress-coping response), which results in a 'current' inability to escape stress when there is a possibility to do so (Amat et al., 2005; Maier and Watkins, 2010). Animals that are exposed to 'nurture' escapable stress show reduced 'current' learned helplessness compared to animals with 'nurture' inescapable stress experience, reaching the escape level of previously unstressed control animals (Amat et al., 2005; Maier and Watkins, 2010). Likewise, exposure to inescapable and escapable footshock stress during nurture enhances and reduces, respectively, 'current' fear conditioning (Baratta et al., 2008). Fear conditioning is a process during which neutral stimuli (conditional stimuli or CSs) are arranged to predict aversive outcomes such as footshock (an unconditional stimulus or US), leading to CS-evoked learned freezing responses. Conditioned freezing can be considered as a passive stress-coping response, as it protects against the waste of energy and harm when stress is inescapable. In sum, a 'nurture' inescapable stress experience augments 'current' fear learning (1) and impairs escape learning (2), whereas a 'nurture' controllable stress experience impairs 'current' fear learning (3) and

facilitates escape learning (4). All these responses are responses shaped by 'nurture' stress experiences. However, only conditions 1 and 4 involve adaptive responses: 'nurture' inescapable stress experiences promote subjects to passively process threats and reduce the need to relearn about danger, and 'nurture' escapable stress experiences promote escape learning, which allows subjects to escape stress faster in the future. Responses 2 and 3, on the other hand, are maladaptive, because the 'nurture' stress experiences counteract the stress-coping responses that are currently needed. Response 2 corresponds to learned helplessness and may model 'retarded' depression, whereas response 3 reflects agitation and may model 'agitated' depression. This provides the basis for the SCM hypothesis (Fig. 2). Important is that escapable and inescapable stress induce the same magnitude and duration of HPA (hypothalamo-pituitary-adrenal) axis response (Helmreich et al., 1999; Maier et al., 1986), indicating that the stress-coping style that is acquired based on these experiences are not good or bad, but rather reflect different approaches to deal with stress.

To illustrate this interpretation of (mal)adaptive stress responses, it has been shown that low maternal care, causing increased stress-sensitivity and depression vulnerability in later life (Liu et al., 1997; Oakley Browne et al., 1995; Oakley-Browne et al., 1995), was associated with increased hippocampus-dependent contextual fear conditioning in rats (Bagot et al., 2009; Champagne et al., 2008). Whereas this could be considered as a negative outcome, it could also be interpreted as an adaptive maternal effect. This means that mothers may maximize their own fitness by adjusting their offspring to expected future environmental conditions. However, parents cannot always predict the future, and maladaptive responses may emerge when individuals showing strong conditional responses are exposed to environmental conditions that mismatch their nature and nurture. As discussed in the next section, serotonin transporter (5-HTT) gene variation may play an important role in this process.
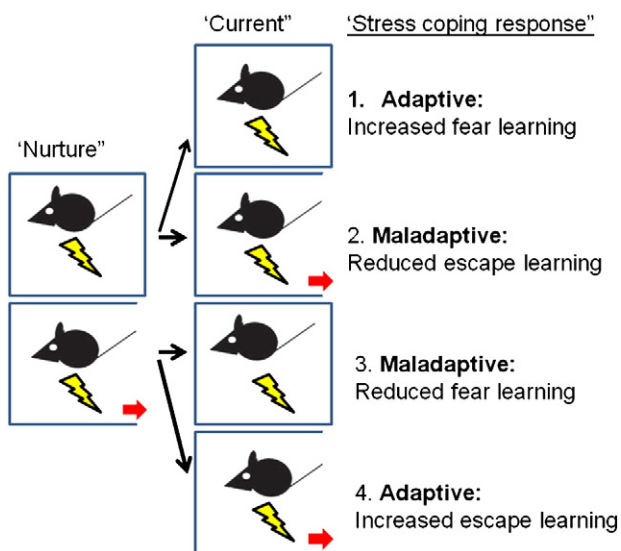
Fig. 2 – Interaction between 'nurture' and 'current' escapable and inescapable stress conditions and possible stress-coping responses in adult rats. Red arrow indicates escapable stress.

3. 5-HTT gene variation

A model par example for nature×nurture interactions in psychiatry is the serotonin transporter-linked polymorphic region (5-HTTLPR) in humans. It consists of two allelic variants, of which the low activity (short; s) allele is associated with reduced transcription of the Slc6A4 gene compared to long (l) allele (Heils et al., 1996). Given that the 5-HTT is responsible for the reuptake of serotonin after its release into the synaptic cleft, the s-allele may be associated with increased extraneuronal serotonin levels in the brain. Whereas evidence is lacking in humans, it has been well established that 5-HTT knockout rodents—which have been accepted as 5-HTTLPR s-allele model (Caspi et al., 2010; Homberg and Lesch, 2010)—show a gene-dose-dependent increase in extraneuronal serotonin levels in various brain regions (Kalueff et al., 2009). This may lead to neurodevelopmental changes, as well as changes in the connectivity between specific brain regions. Relevant in the framework of the SCM hypothesis is that the s-allelic variant of the 5-HTTLPR and 5-HTT knockout in rats and mice is associated with anxiety-related traits (Lesch et al., 1996), and increased responsiveness to stress throughout life time (Carola et al., 2008; Casey et al., 2011; Heiming et al., 2011; Jansen et al., 2011; Nietzer et al., 2011; Schipper et al., 2011; Van den Hove et al., 2011), although some controversial data have been obtained. That is, some studies failed to find increased risk for depression in 5-HTTLPR s-allele carriers exposed to early life stress (Risch et al., 2009). Part of these controversial data may be attributed to the 'for-better-and-for-worse' phenomenon, as the absence of stress or positive environmental conditions may trigger the best outcomes in these subjects (Belsky et al., 2009; Branchi, 2011; Ellis et al., 2011; Homberg and Lesch, 2010). Yet, these controversial data may also be explained by the SCM hypothesis.

The early finding of Caspi et al. (2003) that early life stress leads to increased risk for depression in later life can be interpreted as a Diathesis-Stress/Dual Risk nature×nurture interaction. Yet, the SCM hypothesis considers this as a mismatch between 'nurture' inescapable stress and 'current' escapable stress conditions. Thus, in early life s-allele carriers may have acquired a passive stress-coping response, and the programmed release of a passive stress-coping response in response to current escapable stressors may lead to learned helplessness. This may explain why early life stress exposure in 5-HTTLPR s-allele carriers does not always lead to an increased risk for depression: it is dependent on the nature of current stress conditions. Furthermore, it has been demonstrated that s-allele carriers observing a person undergoing fear conditioning experienced enhanced autonomic responses, showed increased autonomic responses when subsequently exposed to fear themselves (Crisan et al., 2009). In this example there is a match between 'nurture' and 'current' inescapable stress exposure, and thereby the stress-coping response is adaptive rather than maladaptive. s-Allele carriers also have an increased ability to avoid penalizing stimuli when it is possible to do so (Finger et al., 2007), but in this case past stress exposure was unknown. These findings illustrate that the 5-HTTLPR s-allele is associated with increased

adaptive and maladaptive stress-coping responses, which parallels the 'for-better-and-for-worse' concept (see Section 1).

This is also seen in 5-HTT knockout (5-HTT$^{-/-}$) mice. That is, adult 5-HTT$^{-/-}$ mice develop increased learned helplessness after 'nurture' inescapable shock pre-exposure (Muller et al., 2011; Pryce et al., 2012), and forced swim stress during nurture leads to increased passive responding during a 'current' forced swim test (Wellman et al., 2007). Whereas the first is maladaptive, the latter can be interpreted as adaptive because it saves energy under inescapable stress conditions. Yet, to obtain further support for the SCM hypothesis stress responses in association with 'nurture' escapable stress experiences remain to be investigated.

4. The prefrontal–amygdala circuit

An important neural circuit mediating (mal)adaptive stress responses involves the prefrontal cortex (PFC)–amygdala circuit. In 5-HTTLPR s-allele carriers the PFC and amygdala are hyper-reactive to environmental stimuli (Fallgatter et al., 1999; Hariri et al., 2002; Heinz et al., 2005). The central nucleus of the amygdala modulates switches between active and passive emotional states (Gozzi et al., 2010), and the PFC biases attention to behaviourally relevant representations at the expense of behaviourally irrelevant representations (Bishop, 2007). More specifically, neuroimaging studies have revealed that amygdala responses are increased when subjects view threat-related stimuli, while individual differences in PFC recruitment and control over the amygdala determine the attentive bias towards these threat-related stimuli (LaBar et al., 1998; Phelps et al., 2004). In s-allele carriers the attentional bias to stress-related stimuli during nurture might be increased, leading to increased acquisition of passive or active stress-coping responses. In support, recent studies show that s-allele carriers are faster than long (l) allelic homozygotes to pick up fear responses in a fear-conditioning paradigm (Lonsdorf et al., 2009), and show attentional bias to negative (and positive) stimuli (Fox et al., 2011). Once acquired, these 'programmed' responses may be very persistent due to the functional uncoupling between the PFC and amygdala (Pacheco et al., 2009; Pezawas et al., 2005), a pathway involved in extinction (Sierra-Mercado et al., 2011). Finally, due to increased PFC-mediated attentional bias these responses may be quickly released upon stress re-exposure. The nature of the recruitment of the PFC may then determine whether a passive or active (Gozzi et al., 2010) stress-coping response is produced by the amygdala. The amygdala is hyper-reactive in 5-HTTLPR s-allele carriers (Canli and Lesch, 2007; Hariri et al., 2002), which may explain the predicted 'for-better-and-for-worse' (mal)adaptive stress-coping responses in subjects characterized by inherited 5-HTT down-regulation (see also Section 3).

These human imaging findings parallel functional and morphological changes in 5-HTT$^{-/-}$ rodents showing anxiety and depression-related phenotypes (Kalueff et al., 2009). For instance, knockout mice exhibit increased spine density of several dendritic compartments of amygdaloid pyramids (Nietzer et al., 2011; Wellman et al., 2007). Pyramidal neurons

in the infralimbic cortex either display tendencies towards shorter (Nietzer et al., 2011) or longer (Wellman et al., 2007) apical dendritic branches. The seemingly contradictory findings in the PFC may relate to the stress history of the animals. A recent study revealed that increased conditioned fear during recall in 5-HTT$^{-/-}$ mice was associated with increased regional cerebral blood flow in the amygdala, insula, and barrel field somatosensory cortex, decreased regional cerebral blood flow of the ventral hippocampus, and conditioning-dependent alterations in regional cerebral blood flow in the medial prefrontal cortex (prelimbic, infralimbic, and cingulate), as measured by [^{14}C]-iodoantipyrine functional brain mapping (Pang et al., 2011). In general terms, it appears that the amygdala is hyper-reactive across all conditions, whereas PFC activity varies along with experimental conditions, which is well in line with the hypothesized function of the PFC in stress-coping responses.

Amat et al. (2005) showed that temporal inactivation of the ventromedial part of the medial PFC (vmPFC) mimicked the effects of 'nurture' inescapable stress exposure in animals that were actually exposed to escapable stress conditions, and resulted in learned helplessness under 'current' escapable stress conditions. Exposure to inescapable stress during nurture was associated with increased serotonin release in the dorsal raphe nuclei (the origin of serotonergic neurons) (Amat et al., 2005) and amygdala (Christianson et al., 2010). These findings illustrate that the vmPFC controls amygdala responsivity, and thereby the type of stress-coping response that is released. Although a direct comparison with 5-HTTLPR s-allele brain phenotype cannot be made, the brain mechanism involved in behavioural control as shown by Amat and colleagues may resemble the 5-HTTLPR s-allele PFC-amygdala uncoupling. If this brain phenotype can also be translated to 5-HTT$^{-/-}$ rodents, it may explain increased learned helplessness in these animals (Muller et al., 2011; Pryce et al., 2012). It is therefore highly interesting to merge the two research lines and elucidate the impact of 5-HTT gene variation on vmPFC functioning in stress-coping responses.

5. Age-dependent stress-coping responses

The former section highlighted the role of the PFC in controlling amygdala-mediated active/passive stress-coping responses. As more primitive organisms have a more limited behavioural repertoire to cope with stress, it may be that this is due to a lack of PFC-mediated control. This is also the case in infants, and to a lesser extent in adolescents. Rat fear extinction studies have revealed that fear extinction in 'infant' postnatal day [P] P17 rats relies on memory erasure instead of new learning (Kim and Richardson, 2010). This is reflected by the finding that extinction in adult and periadolescent P24 rats, but not in P17 rats, is GABA- and N-methyl-D-aspartate dependent (Harris and Westbrook, 1998; Kim and Richardson, 2007; Santini et al., 2001), and that the PFC is critical for long-term extinction in P24 and adult rats, but not in P17 rats (Kim et al., 2009; Sierra-Mercado et al., 2006). The neural mechanisms underlying extinction in P24 and adult rats may be similar (Kim and Richardson, 2010), as it has been reported that preadolescent (i.e., P24), adolescent (P35),

and adult (P70) rats express identical extinction acquisition following CS and shock pairings. However when tested the next day for extinction recall, adolescent rats showed an almost complete failure to maintain extinction of CS-elicited conditioned freezing compared with P24 and P70 rats (Kim et al., 2011; McCallum et al., 2010). The impaired fear extinction recall across developmental stages has been related to decreased levels of phosphorylated mitogen-activated protein kinase (pMAPK) in the infralimbic cortex in adolescent rats compared to P24 and P70 rats. Extensive extinction training in adolescents increased pMAPK levels (Kim et al., 2011), as well as the recall of the extinction memory (Kim et al., 2011; McCallum et al., 2010), indicating that adolescents are less efficient in utilizing prefrontal areas due to decreased pMAPK levels. Considering fear extinction as an active response as opposed to passive freezing, it is tempting to speculate that the PFC-independency in infants and diminished PFC-mediated top-down control in adolescents undermine an active stress-coping response. This may also be the case in 5-HTTLPR s-allele carriers, because the PFC–amygdala uncoupling resembles the adolescent brain phenotype (Casey et al., 2011). As a result, adults may show mismatches when an active or passive stress-coping response is used under inescapable or escapable stress conditions, respectively, as shown in Fig. 2. Yet, infants and adolescents, as well as 5-HTTLPR s-allele carriers, may be biased to passive stress-coping responses, which limit the repertoire of stress-coping responses and either match current inescapable stress conditions (leading to adaptive responses), or mismatch current escapable stress conditions (leading to maladaptive responses).

6. Implications of the stress (mis)match hypothesis

Sections 2 to 5 discussed the nature×age-dependent nurture aspects of the SCM hypothesis and their possible mechanistic accounts. Although several pieces of evidence are still missing, this way of thinking about nature×nurture interactions may be helpful to identify subpopulations of depressed patients and work towards individualized therapies.

Depression is a heterogeneous neuropsychiatric disorder, and it is unclear what factors and/or biomarkers define different subtypes of depressed patients. The SCM hypothesis may identify the following three depression subtypes: 1) Those showing agitated depression (major depressive disorder with psychomotor agitation) may adopt an active stress-coping response and may have difficulties in handling inescapable stress conditions (e.g. suicide attempts). 2) Patients showing retarded depression (major depressive disorder with psychomotor retardation) may be characterized by a passive stress-coping response, and thereby experience problems with escapable stress conditions (i.e. learned helplessness). Finally, 3) individuals diagnosed with agitated-retarded depression (major depressive disorder with psychomotor agitation and retardation within an episode) may display active/passive stress-coping responses alternately (Leventhal et al., 2008). Potentially this is explained by changes in stress conditions the subjects are exposed to. Depending on the stress-coping response and stress conditions, it might be possible to develop a cognitive behavioural therapy in which

awareness of the out-of-context stress-coping response is increased and addressed. Re-matching of 'nurture' and 'current' stress conditions could be another approach. In either case, insight in the type of patient is needed. Together, understanding the factors contributing to individual differences in stress-coping responses ultimately could help to design individualized therapies.

7. Conclusion

Given the focus in psychiatric genetics on genetic vulnerability and environmental adversity, it may be not surprising that the possibility that genetically-driven stress responses can also be adaptive has gone unnoticed. As outlined in this essay, more appreciation of (mis)matches between programmed stress-coping responses and current stress conditions may lead to advances in nature×nurture disorders such as depression. Owing to the inherent limits of human studies, both in terms of what has been measured (escapable/inescapable stress) and how the data have been analyzed and presented in primary publications, it is currently impossible to support the SCM by current human data. Furthermore, rodent studies are biased towards stress-related tests that cannot clearly be denoted as escapable or inescapable (elevated plus maze test, open field test, social interaction test), which hampers the interpretation of nature×nurture studies that are emerging (Carola et al., 2008; Heiming et al., 2011; Jansen et al., 2011; Nietzer et al., 2011; Schipper et al., 2011; Van den Hove et al., 2011). This essay may trigger a more sophisticated analysis of the type of stressors subjects are exposed to, to enable a better interpretation of findings.

To provide a mechanistic account for the SCM hypothesis, I focused on the PFC and amygdala in a very simplistic manner. Obviously, networks involved in passive and active stress-coping are far more complex and not only involve specific PFC and amygdala subregions, but also the dorsal raphe nucleus (Amat et al., 2005), periaqueductal gray and hypothalamus (Bandler et al., 2000), and dorsal striatum (Strong et al., 2011). In addition, whereas the 5-HTTLPR was taken as example for the SCM hypothesis, other polymorphisms like gene variants in the GABA(A) receptor, the mu-opioid receptor, catechol O-methyltransferase (COMT), monoamine oxidase (MAOA), the alpha(2)-adrenergic receptor, brain-derived neurotrophic factor, the angiotensin-converting enzyme, the high-affinity mineralocorticoid receptor (MR), and the lower-affinity glucocorticoid receptor (GR) (Derijk, 2009) may affect (mal)adaptive stress-coping responses as well. It is also important to note that epigenetic modifications are likely involved in the programming of stress-coping responses by nature×age-dependent nurture interactions, and their elucidation may lead to other interventional approaches targeting enzymes involved in these epigenetic modifications, such as DNA methyltransferase inhibitors and histone deacetylase inhibitors. Finally, if the SCM hypothesis will be supported by future studies, it may not only bring advances in depression-related research, but also may have implications for other psychiatric conditions caused by nature×nurture interactions, such as schizophrenia, and drug dependence. With human and non-human primate 5-HTTLPR s- and l-allele carriers, as well as 5-HTT knockout

rodents, at hand (Homberg and Lesch, 2010) the SCM hypothesis may pose new challenges for future research.

Acknowledgments

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