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BRAIN RESEARCH

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