Mismatch or cumulative stress: Toward an integrated hypothesis of programming effects

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This paper integrates the cumulative stress hypothesis with the mismatch hypothesis, taking into account individual differences in sensitivity to programming. According to the cumulative stress hypothesis, individuals are more likely to suffer from disease as adversity accumulates. According to the mismatch hypothesis, individuals are more likely to suffer from disease if a mismatch occurs between the early programming environment and the later adult environment. These seemingly contradicting hypotheses are integrated into a new model proposing that the cumulative stress hypothesis applies to individuals who were not or only to a small extent programmed by their early environment, while the mismatch hypothesis applies to individuals who experienced strong programming effects. Evidence for the main effects of adversity as well as evidence for the interaction between adversity in early and later life is presented from human observational studies and animal models. Next, convincing evidence for individual differences in sensitivity to programming is presented. We extensively discuss how our integrated model can be tested empirically in animal models and human studies, inviting researchers to test this model. Furthermore, this integrated model should tempt clinicians and other intervenors to interpret symptoms as possible adaptations from an evolutionary biology perspective.

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1. Adaptive phenotypic programming

From animal research we know that environmental cues can steer development in a direction that is adaptive in the expected later environment: adaptive phenotypic plasticity [1]. A famous animal example of adaptive programming is the Bicyclus butterfly [2]. When it pops in 18 °C it is equipped to survive a long dry season; when it pops in 25 °C the butterfly will be equipped to live in a warm and wet environment. The phenotype is adaptive to the expected later environment. A mismatch between the expected later environment and actual circumstances decreases chances for survival and reproduction [3]. This example is very simple in the sense that only one cue is sampled within a very short critical period, and that this cue discriminates between future environments very well, because temperature...
reliably predicts season. In species with longer life spans it is less likely that cues have such high discriminative power [4], making it necessary for animals to sample multiple cues [5] and to integrate information from different cues [6]. Still, there is a lot of evidence that animals and also humans adjust their phenotypes based on information they gathered from their early environments [4,7–12].

When it comes to the effects of adverse environmental stimuli on individual health there are two main and seemingly contradicting views. The more traditional hypothesis is the “cumulative stress” hypothesis, where aversive experiences early in life predispose individuals to be more vulnerable to aversive challenges later in life (Fig. 1A). This hypothesis is sometimes also referred to as “2-hit” hypothesis [13,14], although the term is a bit misleading, as it suggests the necessity of 2 specific stressful events, or a limitation of 2 (and not more) of those events. In this hypothesis the effects of stress exposure during a lifetime are cumulative and lead to the build-up of allostatic load, which would increase the likelihood of developing a disease. The cumulative stress hypothesis is based on a deterministic (psycho)pathological model, in which deviations from (social) norms define what is seen as pathological [15]. The more stress exposure, the worse the outcome [16]. The mismatch hypothesis (Fig. 1B), on the other hand, states that aversive experiences early in life trigger adaptive processes, thereby rendering an individual to be better adapted to aversive challenges later in life [17,18]. Thus, according to the mismatch hypothesis, an individual who has experienced high levels of psychosocial stress early in life is programmed for dealing with high psychosocial stress and is therefore better off with exposure to high stress levels in later life. The mismatch hypothesis is therefore a context specific hypothesis in which the costs or benefits of a trait depend on the context. This is a provocative hypothesis, because the prevailing idea in the literature of the last decades is that cumulative stressors leads to a “wear and tear” of physiological systems and is bad for your health [19–21].

There are a great variety of conditions and situations that can be perceived as stressors and will elicit a stress response. Because in Western societies stressors related to psychopathologies are mainly psychosocial in nature, the focus of the present paper is on psychosocial stress. An extremely large body of evidence shows that psychosocial stress indeed contributes to psychopathology, for example depression [22–24]. In the following chapter examples of evidence for the adverse effects of psychosocial stress are given, ranging from stressors in the prenatal environment, through childhood and adolescence to adulthood.

2. Observational studies in humans

Starting with the prenatal environment, maternal stress and especially maternal anxiety during pregnancy have proven to be robust predictors of behavioral and emotional problems in the offspring [25–27], the effects of which seem to last at least into adolescence [28–30]. Maternal anxiety has also been associated with impaired cognitive performance [31] and altered HPA axis functioning [32].

An example of a human model for investigating a mechanism through which the prenatal psychosocial environment affects the phenotype is the investigation of fetal cortisol exposure by studying the effects of licorice consumption during pregnancy [33,34]. The main ingredient of licorice, glycyrrhiza, inhibits the function of a placental enzyme that normally acts as a barrier to maternal cortisol [35]. Therefore, high licorice consumption during pregnancy exposes the fetus to higher levels of maternal cortisol than normal. Indeed, alterations in HPA axis functioning of eight year old offspring of mothers who consumed more than 500 mg of glycyrrhizin in licorice per week have been shown [34]. Additionally, high maternal licorice consumption has been associated with attention problems and aggressive behavior [33]. More direct evidence for the role of the placenta in prenatal programming is now emerging [36]. However, the observed effects of high cortisol exposure of the fetus can be interpreted both as predisposition for disease (cumulative stress hypothesis) or as adaptive programming to prepare the offspring for a probably short and harsh life under aversive circumstances (mismatch hypothesis).

A large body of literature shows that child maltreatment is associated with later psychopathology [37–39]. More common stressors, such as parental divorce [40–43] or low socioeconomic status during childhood [44,45] are associated with psychopathology as well. The same can be said for stress during adolescence [46–49] and adulthood [23,50,51]. Please note that in all above cited examples maladaptations are defined as deviations from the norm, while in another context, these traits could be adaptive. In this respect, one should not be surprised that effect sizes are generally small to modest and that there are huge inter individual differences in outcomes [52–56]. In other words, stress is neither determinative nor sufficient in explaining psychopathology [57,58].

A logic follow-up would be to study the interaction between stress in early life and adulthood [59]. In light of the huge literature into main effects of psychosocial stressors on psychological functioning, the amount of research published on the interaction between
psychosocial stressors in different periods of life is scarce [59]. Nomura and Chemtob [60] investigated how low birth weight interacted with childhood abuse in predicting psychological problems in adulthood. Costello and colleagues [61] investigated how low birth weight interacted with both childhood and adolescent stressors such as poverty, abuse and parental separation. A major problem with these studies in terms of interpretation in light of the cumulative stress hypothesis or the mismatch hypothesis is the fact that the ‘second hit’ occurred either in childhood or adolescence. Both the prenatal period and childhood have traditionally been seen as so-called windows of opportunity, time periods during which the individual is highly susceptible to phenotypic programming [7,62–64]. Evidence for adolescence as another possible period for programming is emerging in animal studies [65–69] and human studies [30,70]. Laceull and colleagues showed that temperament traits were target of programming by stressful life events between 11 and 16 years of age [70]. In another study, Laceull and colleagues showed that the effects of stressful life events were largest in early childhood and pre-adolescence [30]. Thus, the effects of stressors during adolescence could still be interpreted as programming effects, instead of evaluating the outcome in light of the mismatch hypothesis. In animals, the body of literature into the interaction between early and later stress is much larger, although results do not consistently support either the cumulative stress hypothesis or the mismatch hypothesis.

3. Animal models of developmental programming

A number of studies have gathered convincing evidence for the cumulative stress hypothesis. Using the 24-hour maternal deprivation paradigm [71], Choy and colleagues could show that a combination of maternal deprivation with later corticosterone treatment resulted in more pronounced effects on learning and memory, BDNF expression and prepulse inhibition than either treatment alone [13,72]. Similarly, a combination of maternal deprivation with chronic unpredictable stress had additive effects on hippocampal BDNF and NCAM expression [73]. Another often used postnatal stress paradigm in rodents is repeated maternal separation for 3 h from postnatal days 1 to 14 [74]. Animals exposed to maternal separation showed a higher sensitivity to dextran sulfate sodium-induced severe colonic inflammation [75], stronger social-defeat induced anhedonia [76] and more passive stress coping as well as increased anxiety following social defeat [77]. Further, prenatal restraint stress in rats increased vulnerability to chronic restraint stress in adulthood in male offspring, leading to increased anxiety and increased ACTH plasma concentrations [78].

On the other hand, there is also substantial evidence for the mismatch hypothesis. Kiank and colleagues showed that mild early life stress in female BALB/s mice increased stress coping ability at 12 weeks of age when exposed to chronic psychological stress [79]. Rats that suffered from neonatal bacterial infection were shown to be less affected by inescapable tailshock stress as adults, indicated by a blunted corticosterone response and less depression-like behavioral symptoms [80], although a similar study showed an increased stress sensitivity in LPS treated rats when measuring lymphocyte proliferation [81]. Further, offspring of low licking and grooming Long-Evans dams displays improved hippocampus-dependent learning and LTP under high-stress conditions in the CA1 [82] and dentate gyrus [83]. Also with the 24-hour maternal deprivation model, there are data supporting the mismatch hypothesis, where hippocampal plasticity and emotional learning under high-stress conditions in adulthood was improved in maternally deprived offspring [84]. On the behavioral level, Ellenbroek and Cools reported that only a maternal deprivation or social isolation alone significantly suppressed prepulse inhibition, but when both conditions were combined the animals behaved as unstressed controls [85].

In addition to those studies favoring clearly one over the other hypothesis, there are also studies that seemingly support both hypotheses. For example, rats exposed to 3 h maternal separation from postnatal days 2 to 12 responded as adults to 21 days of 6-hour daily restraint stress with a blunted response on thymus and adrenal weight as well as a lesser reduction in CA3 apical dendritic length compared to restraint rats without the history of maternal separation [86]. On the other hand, only rats that experienced both maternal separation and chronic restraint displayed increased anxiety in the elevated plus maze test. Similarly, neonatal LPS exposure was shown to enhance the anxiogenic effect of repeated restraint stress in male rats, while the corticosterone response to a novel environment is normalized in rats that were exposed to LPS as neonates compared to saline-treated restraint rats [14]. Again, it is important to point out that all of the above mentioned phenotypic alterations need to be interpreted in relation to specific environmental contexts. While deviations from the norm (e.g. higher HPA axis (re)activity, increased anxiety, more passive stress coping, etc.) are usually seen as maladaptive and ‘disease-like’. The same traits can be highly adaptive depending on the environmental context.

When considering those data in the light of the cumulative stress and the mismatch hypothesis, it is important to note that none of these studies considered the impact of genetic predisposition on the outcome of the study. Heiming et al. recently reported that offspring of mouse mothers exposed to aversive olfactory cues during pregnancy and lactation are more anxious compared to controls, suggesting an adaptation of the offspring to a more aversive environment [87]. Interestingly, this effect was most pronounced in animals lacking the 5-HTT, demonstrating that different genetic predispositions are able to modulate the programming effect of early life stress, those animals were unaffected. The important role of the genetic background was also nicely demonstrated by van der Veen and colleagues, demonstrating that the long term effects of poor maternal care on cocaine intake and stress-coping behavior are mouse strain dependent [88]. Further, in animals with a dysfunction of the glucocorticoid receptor in the pituitary, which resulted in high corticosterone exposure during postnatal development, the effects of chronic stress during adulthood were shown to be ameliorated [89].

4. Individual differences in sensitivity to early programming

Both in animal and human studies evidence for genetic polymorphisms as a source of individual differences in sensitivity to the early environment is growing, for example in the serotonin transporter gene linked promoter region (5-HTTLPR) [90,91]. This type of evidence contributes to explaining why inter individual differences in the outcomes of stress are so high. Belsky and colleagues proposed that specific genes or genetic variants may predispose an individual to be more susceptible to environmental influences, thus increasing the individual level of plasticity [92]. As the term plasticity is ambiguously defined across different research disciplines, we here prefer to use the term programming sensitivity. It can be defined as the ability of an individual to adapt its phenotype in response to environmental cues to increase its fitness under similar environmental conditions in the future. Additionally, it increasingly becomes clear that those features that determine an individual’s susceptibility to negative aspects of the environment, also determine susceptibility to positive aspects of the environment [93–97]. From this perspective, those susceptibility genes are not just ‘bad guys’ [92].

It is therefore conceivable that both the mismatch and the cumulative stress hypothesis can be accurate given a certain individual programming sensitivity (Fig. 2). Individuals with a high programming sensitivity should therefore benefit from a match of early life and adult environment, even if both are aversive, while in individuals with a lower responsiveness and adaptability to environmental contexts the same situation would result in a continuous wear and tear.

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of the system and consequently disease. A similar idea was captured by the “3-hit hypothesis” suggested by de Kloet et al., where the first “hit” would actually be a specific genetic background [98,99].

Next to the more recent focus on genetic polymorphisms, human literature has focused on two other types of individual characteristics determining differences in sensitivity to early programming: behavioral and physiological reactivity. The focus of early plasticity, or differential susceptibility for better and for worse, as determined by genetic polymorphisms has mainly focused on dopaminergic and serotonergic pathways [92,93,100,101], although genes involved in neuroplasticity are likely candidates as well [102,103]. Where early plasticity concerns behavioral reactivity, early childhood temperament has received most attention. Results from this field seem very consistent: children with difficult temperaments show higher susceptibility to negative as well as positive aspects of their environment [96].

High physiological reactivity has also been hypothesized to indicate high susceptibility to environmental influences [94,95]. Indeed, highly reactive individuals have been found to have greater susceptibility to a number of different aspects of the environment, including father involvement, parental supportiveness, teacher characteristics and family adversity, with a number of different outcomes including mental health, prosocial behavior and pubertal development [104–107].

The interesting feature of both behavioral and physiological reactivity for the mismatch hypothesis is that they are programmable themselves [94,95,104,109]. In their theory of Biological Sensitivity to Context, which is a theory of differential susceptibility [96], Boyce and Ellis [94,95] hypothesize that mainly children in either highly supportive environments or very harsh, unpredictable environments will adapt their phenotype to increase chances of success in their particular niche. Thus, not only heritable variation but also developmental experience determines early plasticity or programming effects [96].

Another issue that determines whether an individual is programmed by his or her early environment is timing. As was argued in Section 3, evidence suggests that the pre-natal period, early childhood and adolescence or puberty are so-called windows of opportunity [62]. In addition to the time window of stress exposure, the long term effects of (combined) stressors may also not be stable or unidirectional and may vary over the course of the life span [110]. Thus, combination of three factors: Heritable variation, developmental experience and the timing of experience determine the size of programming effects in each individual. For example, individuals with a highly susceptible genetic background but growing up in a moderately supportive, moderately stressful environment are not expected to experience large programming effects, neither are individuals lacking genetic susceptibility growing up in an extreme environment, nor are genetically susceptible individuals experiencing an extreme environment outside the windows of opportunity.

From an evolutionary perspective these differences in programming effects are not surprising, because individuals are expected to adapt to an ecological niche [111]. Individuals within species will show adaptations to this niche not only to enhance survival, but also to adjust their reproductive strategy [112]. Because the future is uncertain, differences in the size of programming effects within families are not surprising either. Chances of survival for at least part of the offspring increase when children within a family are different [113,114]. Interestingly, recent studies also highlighted robust inter-individual differences within one litter in rodents [115,116]. Only individuals who were substantially programmed by their early environment are expected to benefit from a match with later environments and suffer from a mismatch [18]. Individuals who were not substantially programmed are expected to show average performance and health in most environments. Integrating the cumulative stress with the mismatch hypothesis using this third axis of programming sensitivity (Fig. 2), the mismatch hypothesis is expected to apply to individuals who were programmed for a specific environment, while the cumulative stress hypothesis is expected to apply to individuals who did not experience large programming effects.

4.1. Evolutionary limits to developmental programming

An important notion is that adaptiveness of developmental programming is limited. Natural selection has taken place over extremely long periods of time and has relied on predictability of environmental factors [4,6]. Obviously, adaptation to new environmental factors that were not present during the thousands of years of natural selection.
has not yet taken place, as it is beyond the range of environments encountered during evolution. Environments that are beyond those limits can 1) contain factors that were consistently absent during the process of natural selection or 2) lack factors that were consistently present during this process.

An example of the first, meaning environmental adversity for which an evolutionary solution has not been developed, could be extremely depriving orphanages as seen in Eastern Europe [117]. Children who were reared in those orphanages and were subsequently adopted into above-average UK families between infancy and 3½ years of age have been studied until pre-adolescence. Although a remarkable catch-up occurred, significant problems in psychological functioning remained visible at age 11 relative to children who had not been institutionalized and adopted before 6 months of age [118,119].

An example of the second situation, where factors that were consistently present during the process of natural selection are now absent, is the hygiene hypothesis. Increased prevalence of, for example, major depression, is attributed to the absence of certain microorganisms in modern societies that were consistently present during the past thousands of years [120]. Raison and colleagues hypothesize that the development of our immune system has 'learned' to rely on certain microorganisms present in mud, untreated water and unwashed food, so-called old friends. Lack of training of the immune system due to the absence of those microorganisms, which is caused by increased hygiene, would lead to pro-inflammatory reactions to psychosocial stressors promoting depressive symptoms [120]. Other examples are breast feeding, exercise, fatty acids and age-mixed socialization [121]. In such cases of evolutionary mismatch it is unlikely that the physiological and behavioral consequences are fully adaptive in the later environment.

5. Testing the mismatch hypothesis

To answer the question whether psychosocial stress has the capacity for adaptive programming of the human phenotype researchers need to compare four groups that differ in (dis)continuity of social stress on adaptive capacity and health outcome (Fig. 3): A group that had high stress exposure in both early and later life (path a), a group that had low stress exposure in early and later life (path d), and two groups that had different stress levels in early and later life (paths b and c). Individuals with a high genetic susceptibility, who grew up in an environment with high psychosocial stress (paths a and b), will be programmed for dealing with highly aversive environments. These effects are assumed to persist throughout life. Individuals for whom the later environment does not match early environment (paths b and c) are expected to display a maladapted phenotype, resulting in a higher risk for disease [9,17,18,21,96,111,122]. Importantly, this hypothesis should apply only to those who were substantially programmed by their early environment, while the cumulative stress hypothesis would apply to those who were only programmed to a small extend (Fig. 2).

There are a number of challenges involved in testing this integrative hypothesis in animal models as well as in human observational studies. First, it will be important to select environmental manipulations with high ecological validity in animal studies, or, equivalently, measure relevant aspects of the human environment, both early in life as in adulthood. Second, careful phenotyping will have to take place in both animals and humans to measure programming effects. Alternatively, individuals could be subgrouped in high versus low plasticity cohorts, to test the hypothesis that predominantly high plasticity individuals benefit from matched environments, while low plasticity individuals would benefit from a low overall exposure to adversity. Third, another round of careful phenotyping should take place in a later stage of life, to measure the relevant outcomes of different combinations of early and later environments in individuals who differed in their sensitivity to early programming. Finally, care should be taken to avoid interpreting deviations from the norm automatically as maladaptive, and rather interpret the data in the light of the environmental context.

5.1. Relevant aspects of the environment

From an evolutionary perspective the main characteristics of the environment that should shape adaptive phenotypes are harshness, unpredictability and resource availability [112]. Ellis and colleagues reviewed extensive evidence from different species on how environmental harshness and unpredictability shape differences in life history strategies both between and within species. They convincingly argue that the rate at which external factors cause morbidity and mortality, referred to as environment harshness, and the variation of environmental harshness over time and space, referred to as unpredictability, steer both the evolution and the development of differences in life history strategies. At the extremes of the life history strategy continuum fast versus slow strategies can be distinguished [113]. Those strategies differ in the growth rate of the child, the timing of puberty and sexual debut, the timing of birth of the first child, the number of sexual partners, the number of children and the parenting style. Additionally, a number of traits related to increasing chances of survival should develop in line with those reproductive traits.

In Western societies, the most salient cues for environmental harshness are socioeconomic status, quality of parental investment, neighborhood disorder and violence, while environmental unpredictability, at least in childhood, is best measured as the number of parental changes and the number of house moves [112]. Indeed, socioeconomic status, neighborhood disorder and quality of parental investment have proven to be robust predictors of life history related traits such as pubertal development, sexual activity, teenage pregnancy and number of children [123–127]. More recently, the focus

Fig. 3. Suggested study design to test the mismatch hypothesis. Researchers would need to compare 4 groups (a–d), which differ in their (dis)continuity of environmental conditions during development and in adulthood. Further, these groups should consist of individuals with a proposed high programming sensitivity, and the early environmental exposures should occur during highly plastic developmental phases.
phenotype in the school environment may be outweighed by the environment the individual lives in, in order to judge its costs and effectiveness of a phenotype should be evaluated across the whole range of environments. One of the main factors that have shifted to investigating the interrelationship between those features. In animal models, it has been shown that environmental harshness and unpredictability are essential core features of animal models for psychiatric disorders. In rodents, environmental harshness is usually modeled by exposing the animals to aversive situations, including cold, infections, or a high degree of social instability. During the postnatal period, maternal behavior can be modulated by removing the mother from the litter, variations in maternal care, or by manipulation of the maternal environment. Also in other species there are many examples in the literature where environmental harshness with a certain degree of unpredictability and uncontrollability are used. These range from social instability in guinea pigs to poor maternal nutrition in sheep or pigs to manipulation of foraging conditions in Bonnet macaques. All of these manipulations have in common that they aim at specific developmental windows of opportunity, induce a chronic stress situation in the mother and/or the offspring and are to a certain extent unpredictable or uncontrollable.

5.2. Measuring programmed (endo)phenotypes

Apart from effects on maturation and reproduction, the early environment should also program individuals for enhanced survival related traits. Because reproductive success is hard to model in the lab, survival related traits have usually been target of investigation in animal models. For example, anxiety and depression-like behaviors have been target of investigation in different animal models discussed in Section 4. Although these behavioral phenotypes might be interpreted as adaptive in harsh, unpredictable environments, they are interpreted as maladaptive in mainstream society. In 1991, Belsky, Steinberg and Draper suggested that symptoms of anxiety and depression (especially in females) and symptoms of aggression (especially in males) could be traded off from fast life history strategy, the strategy that gives highest chance for survival of offspring in a highly unpredictable environment: reproduce early and often. As Rutter also notes, features that increase chances of survival in a threatening environment, might actually have negative consequences in an environment without that particular threat. He gives the example of being heterozygote for sickle-cell disease, which is protective against malaria, but we could also think of symptoms of ADHD that are not particularly helpful in the classroom, but might enhance survival in dangerous environments. Thus, psychiatric symptoms, both internalizing and externalizing, should be expected to be high for individuals with early life stress, regardless of the symptoms’ later adaptiveness. On the other hand, the perception of the same symptoms might differ between individuals depending on their present circumstances. These symptoms might not be perceived as problematic by individuals who can use them in their particular niche. Those individuals might be less likely to seek help, even though their symptom level is the same as for another individual in another environment who does seek help from a mental health care professional who perceived these symptoms as problematic. In terms of measurement, this might mean that measuring symptoms with questionnaires is not sufficient. Researchers testing the mismatch hypothesis in human observational studies will need additional measures including information about life circumstances and the perception of the symptoms (see also [146]). One should also note that the adaptiveness of a phenotype might be evaluated across the whole range of environments the individual lives in, in order to judge its costs and benefits. To take the example of ADHD again, the disadvantage of this phenotype in the school environment may be outweighed by the advantage of having this phenotype in an aggressive or abusive family or peer environment.

Another target of programming frequently measured in animal models is learning and memory and related brain plasticity. In humans, maltreated children differ in cognitive processing of emotional expressions compared to children who were not maltreated. Maltreated children recognize angry faces with less information, they orient quicker to but disengage slower from angry faces, they even seem to have a perceptual preference for angry faces. All these adaptations could be interpreted maladaptive in safe, predictable environments, but adaptive in dangerous, unpredictable environments.

Physiological responses to stress have been studied as well as target outcomes in animal models. In humans, programming effects of the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS) are widely studied, because of the proclaimed physiological link between stressors and psychiatric disease, but also because reactivity of these axes is relatively easy to measure. The end product of the human HPA axis, cortisol, can reliably be measured in saliva, while activation of the ANS can be measured using surface electrodes. These non-invasive measurement methods are preferred over invasive methods, especially in large observational studies. Recently, Del Giudice and colleagues have formulated clear hypotheses concerning adaptive programming of these axes. With a low sensitivity to early programming as well as individuals who grew up in a moderately supportive, moderately stressful environment are expected to develop a generalist phenotype. Those individuals are expected to show moderate reactivity of their stress axes, enabling them to cope relatively well with a broad range of environments. In contrast, individuals with high sensitivity to early programming who grew up in either a highly predictable, supportive environment or in a harsh, unpredictable environment develop high reactivity of both the HPA axis and the ANS. Those individuals specialized to do extremely well in their environmental niche. This model might explain some of the differences in findings between studies into, for example, effects of early adversity on programming of the HPA axis. While some researchers report a lower HPA axis response to a social stressor in individuals who experienced early adversity, while others report a higher HPA axis response.

5.3. Testing the full model

For testing the full integrated model of the cumulative stress and the mismatch hypothesis different approaches can be taken. In animal research there has been a long tradition of selecting two (genetically) different lines to compare the impact of environmental manipulations. In human research, however, there is a large emphasis on generalizability to the population as a whole. In animal models, pre-selected lines which differ on susceptibility or plasticity can be compared on the outcomes of the different trajectories.

Although the robustness of information on individual differences in early plasticity in humans is increasing, the evidence is not strong enough to pre-select individuals with high and low programming sensitivity. For example, evidence for a genetic polymorphism in the serotonin transporter region (5-HTTLPR) as a source of differential susceptibility to early life stress but not later life stress is accumulating, as well as the evidence for dopamine related genes. However, explained variance is (yet) too low for these genetic polymorphisms to be used to test the mismatch hypothesis versus the cumulative stress hypothesis in individuals with one or the other genotype. The same is probably true for stress reactivity as a readout of differential susceptibility. Although many studies in children point in the direction of highly reactive children being more sensitive, such moderation effects are usually not reported by

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researchers studying older children or adolescents [158–161], underscoring the importance of the developmental timing of stressors. Another complicating factor using childhood stress reactivity as a variable to distinguish individuals on the level of sensitivity to programming is the time gap that would be needed between measuring childhood reactivity and adult outcomes relevant for the mismatch hypothesis. This problem could be overcome in fast-lived animal models. Next to preselected extremes in plasticity (selective breeding lines, knockout or transgenic animals, etc.), it is also feasible to test large cohorts of genetically variable outbred mice and identify vulnerable and resilient individuals within these cohorts [18,68].

In human observational studies the most feasible approach is probably to measure (endo)phenotypes, which were likely targets of programming by the environment and compare specialists and generalists who followed different trajectories (Fig. 3) on relevant health outcomes. For example, one could compare individuals with high stress reactivity who grew up in positive and negative environments respectively (sensitive and vigilant specialists), to individuals with moderate stress reactivity (generalists). The specialists should have displayed a high level of programming sensitivity to have developed the traits relevant for their niche. In contrast, the generalists should either not have been exposed to an environment that required them to specialize, or they were characterized by a low sensitivity. The specialists would be hypothesized to suffer from a mismatch, while the generalists are hypothesized to suffer from cumulative stress. Another example could be to compare individuals who developed a better ability to sustain attention compared to shifting attention (sensitive specialists) or vice versa (vigilant specialists) to individuals who are equally good at both tasks (generalists). The key to this approach is to select and carefully measure relevant (endo)phenotypes. Although this approach requires large and diverse samples, the advantage of this approach is that it does not rely on a priori assumptions about individual differences in sensitivity to early programming.

6. Implications of the integrated model of cumulative stress and mismatch

The integration of the two seemingly contradicting hypotheses by placing them on different places of a third axis – programming sensitivity – has a number of interesting implications. First, it is not surprising that also without the now proposed theoretical work stress was identified as a risk factor for disease, as also in the integrated hypothesis there is a clear bias for stressful environments increasing the overall disease risk. Our integrated model implies that studies neglecting individual differences in sensitivity to programming are likely to suffer from high variability of the data, as within one study group (e.g. exposure to early trauma) both hypotheses could apply and result in opposite outcomes. Related to this, the low explained variance found so far for genetic risk factors identified by single gene association studies and even genome-wide association studies (GWAS) makes sense, as a risk allele under one environmental condition would at the same time bestow the carrier with an advantage in another environment or life trajectory.

Secondly, the integration of the cumulative stress hypothesis with the mismatch hypothesis has important implications for clinical practice. In light of the cumulative stress hypothesis, clinicians are tempted to focus on maladaptation from a traditional psychopathology perspective. In light of the mismatch hypothesis, clinicians should be enticed to interpret the same symptoms from an evolutionary biology perspective. From a psychopathology perspective socially undesirable behaviors are seen as maladaptive, while the same behavior can be interpreted as adaptive from an evolutionary perspective. Our integrated model enforces clinicians to interpret a patient’s symptoms from both perspectives, taking into account the patient’s past and current environments as well as the programming effects of the early environment for this specific patient.

In terms of prevention of health inequality our integrated model emphasizes the importance of targeting both individuals within a certain environment as well as their environment. Trying to modify a child’s behavior to be adaptive from the psychopathology perspective, might cause a maladaptation from the evolutionary biology perspective. It is unlikely that this intervention is perceived as successful by the participants if their early environments turn out to have reliably predicted their later environments. A mismatch was created by the intervention through changing the phenotype while leaving the environment unchanged.

Taken together, we hypothesize that some individuals are at greater risk for psychopathology when life stress accumulates, while others are at greater risk if a mismatch occurs between their early and later environments. We propose that individual differences in sensitivity to early programming in combination with the environments encountered during sensitive periods determine whether the cumulative stress hypothesis or the mismatch hypothesis is more applicable.

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