Achievements and challenges in the biology of environmental effects

Michael Rutter[1]

Medical Research Council Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London SE5 8AF, United Kingdom

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The starting point for the study of adverse experiences is that some have enduring consequences that continue after the period of exposure to the adversity. That raises four basic issues: whether social adversities can be considered homogeneous, whether the crucial effect lies in the "objective" or subjectively perceived "effective" environment, whether the effects are environmentally mediated, and whether the form of biological embedding involves psychological or health consequences. The findings in the literature are discussed in relation to the biological effects of supposedly positive or normal experiences, the use of natural experiments to determine the causal effects of early experience, the heterogeneity of social adversity, the possible mediators of the biological embedding, gene–environment interdependence, and remaining challenges.

causal inferences | neuroplasticity | epigenetics | sensitive periods

This Arthur M. Sackler Colloquium and the special issue of PNAS based on it deal with the multiple tricky issues involved in the biological embedding of social adversity. The starting point is the evidence that some adverse experiences have consequences that extend far beyond the time when the experiences operate.

The concept of environmental effects raises four other basic issues. First, to what extent can social adversities be considered homogeneous? Are the mechanisms involved in, for example, abuse, neglect, and social disadvantage similar or different (1)? Second, does the crucial effect lie in the "objective" environment or in the subjectively perceived "effective" environment? The query has to be posed because of the abundance of evidence that the individual plays a crucial role in the shaping, selection, and conceptualization of his/her experiences (2). The outmoded notion of environments impinging on a passive organism can be firmly rejected. Third, even though an experience can be appropriately viewed as describing an environment, as with, for example, family break-up or poverty, are the risk effects environmentally (rather than genetically) mediated (3)? That issue emphasizes the crucial importance of considering the research strategies that may be used to test whether it is justifiable to proceed from a statistical association or correlation to a causal inference (4, 5).

The notion of "embedding" means that something is firmly fixed in a larger mass; in this connection, the "something" is an adverse experience and the "larger mass" refers to the biology of the organism. What this means is that the focus excludes purely transient biological effects. Of course, they too will have biological correlates. All operations of the mind, conscious and unconscious (and that includes the perception and conceptualization of experiences), have to be based on the working of the brain. These constitute a matter of considerable broad interest, such as in the extent to which neuroscience should or could influence the operation of the law (6, 7). For example, can neuroscience measures of brain functioning help in deciding whether someone is lying or whether the level of mental capacity is below that required for criminal responsibility? Once more, those issues are outside the scope of this article.

However, the starting point of persistence of effects beyond the duration of the supposed risk experience does raise a further fundamental query. The key point is not the persistence of the biological effects but rather the persistence of the relevant psychological or health consequences. In other words, to what extent do the biological embedding features mediate these broader consequences?

Biological Effects of Supposedly Positive or Normal Experiences

To tackle these questions, it may be helpful to start with what is known about the effects on the brain of positive experiences within the species-typical normal range. It is often claimed that biological embedding occurs more readily during a period of active brain growth (8), but is this so? That could be the case, but both animal models and human studies indicate that biological effects do occur even in adult life after the main period of active brain growth has ceased. For example, the early research into the brain effects in rodents of environmental enrichment concerned adult rats (9–11). There were striking (and opposite) effects on neural structure of environmental deprivation and enrichment. Since then, questions have been raised as to whether the supposed enrichment actually improved on wild state conditions, but what is clear is that positive experiences in adult life definitely had neural effects.

Human studies tell the same story. For example, London taxi drivers who succeeded in passing the rigorous "knowledge" test showed a relative increase in the size of the posterior hippocampus compared with bus drivers or the general population (12). It might be argued that a cross-sectional study such as this could not rule out the possibility that the hippocampal enlargement preceded the learning experience. However, the later finding that retired taxi drivers lost most but not all of the hippocampal changes effectively ruled out that possibility (13). The findings on musical skills are broadly comparable but without the crucial reversal causal test (14, 15). However, the experimental study of the neural effects of learning juggling skills in adult life confirms that causal inference (16). It is evident that the biological embedding of "normal" learning experiences is not confined to an early sensitive period of active brain growth.

On the other hand, other research has shown the importance of developmental phase-specific effects for some experiences. This is most strikingly shown in the Nobel prize-winning research of Hubel and Wiesel (17) on the effects of visual experience on the normal development of the visual cortex. This led Greenough et al. (10) to draw the distinction between experience-expectant sensitive period biological programming effects (i.e., those that are contingent on the occurrence of experiences that are normally expected to be present) and experience-dependent effects (i.e., those that do not

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[1]E-mail: camilla.azis@kcl.ac.uk.

have this sensitive period pattern, as with taxi drivers learning routes). In addition, however, there is the important consideration that development serves the purpose of adapting the organism to the environmental conditions prevailing at the time (18), what Rutter et al. (19) have called "experience-adaptive" programming effects. The most striking medical example concerns the long-term adult health risk effects associated with undernutrition and poor growth in the infancy period (20). The hypothesis is that if the organism is programmed to deal with undernutrition, it is at a disadvantage if faced later with overnutrition. The best established psychological equivalent is the finding that all infants show much the same skills in phonological discrimination up to about 6 mo of age; however, beyond that age, infants show only skills that are relevant to their language of rearing (21, 22). With respect to the developmental phase considerations in relation to the biological embedding of experiences, it will be necessary to consider which pattern (expectant, dependent, or adaptive) applies to the social experiences being considered.

Neuroplasticity refers to the ability of the brain to be molded by experiences or to remodel itself as a response to injury (23–26). Initially, this was considered in relation to "sensitive periods" in early life, but it is now clear that the brain is intrinsically plastic right into adult life, although plasticity reduces with increasing age. The sensitive periods are not as fixed and immutable as was once thought, and they can be extended pharmacologically [as by treatment with a serotonin reuptake inhibitor or administration of norepinephrine (23)]. In addition, plasticity can be increased by vigorous extended exercise. It is adaptive for an organism to be able to regulate plasticity through a series of molecular "brakes" and "accelerators" to ensure both adaptability to changing conditions and stable functioning, and there is a need for a greater understanding of the molecular and cellular mechanisms involved (23).

In summary, there is good evidence for sensitive periods for some sorts of experiences (but not others). However, despite some early claims on the fixity of such periods, it is now evident that they are not immutable; that plasticity extends into adult life, although it diminishes with increasing age; and that intervention can alter plasticity.

Causal Effects of Early Experiences

The study of causal inferences is fundamental to the whole enterprise. There is no point in studying the biological embedding of experiences whose risk effects are not environmentally mediated. It is all too often assumed that the remedy lies in the statistical control of confounders, but numerous studies using "natural experiment" designs have shown that reliance on such statistical control is a seriously flawed approach (4, 5). Nevertheless, there is good evidence that physical and sexual abuse, as well as poverty, does have adverse causal effects. This has been shown by research strategies that deal with the possibility of genetic mediation by using discordant monozygotic twin designs and the possibility of social selection, as, for example, by using population-wide experiences (27, 28). However, there are two important caveats. First, the proximal risk effect may differ from the distal risk being studied. Thus, the benefits of the relief of poverty seem to derive from the consequent effects on family functioning rather than the direct economic benefits for the children (27). Second, some natural experiments indicate that widely accepted causal effects may be wrong. For example, both discordant sibling (29) and assisted conception (30) designs (which contrast methods retaining the genetic link between mother and child, such as sperm donation, and those that do not, such as egg donation) have shown that although prenatal smoking does indeed have a causal effect predisposing to low birthweight, it does not have any appreciable effect on either conduct disturbances or attention deficit hyperactivity disorder (30–32). The same data sets showed that statistical control for confounders did not remove the genetic confound, despite that being the intention.

In summary, there are four main strategies that may be used to test for causal effects. First, there are about a dozen different natural experiments that have been shown to be useful (2, 5, 33). Each involves a set of assumptions and a mixture of strengths and limitations; however, taken together, they have substantial power. Second, there are animal models that allow for experimental manipulation of experiences and, by so doing, provide a strong test of causation. The main limitation concerns the uncertainties regarding extrapolation to human circumstances. Third, there are randomized controlled trials (RCTs). These provide the best test of the internal validity of the causal effect, but there is the major limitation of the need to extrapolate backward in time to what was the actual causal effect before the RCT rather than what could be the causal effect of a new intervention. Fourth, there are human experiments in which social behavior is artificially manipulated. The study by Zink et al. (34) provides an excellent illustration. A computer game was rigged so that the participant thought he/she was competing with either a higher or lower status person. The two situations gave rise to different brain imaging findings. A further example is provided by the use of some kind of intermediate phenotype in which there was a challenge that provoked an immediate response on the same biological pathway as the phenotype of interest. Thus, Hariri et al. (35) used a frightening video to elicit a fear response, the neural effects of which were assessed by brain imaging. Meyer-Lindenberg et al. (36) used a comparable strategy to elicit a response relevant for antisocial behavior. Battaglia and Ogliari (37) used CO_2 inhalation similar to evoke a panic response.

Heterogeneity of Social Adversity and Its Effects

Three other major questions concern environmental effects. First, all studies of all environmental hazards have shown huge heterogeneity in the individual responses with respect to both immediate response and later recovery (38, 39). When considering the biological embedding, a key question therefore is whether the biological feature providing the embedding accounts for this individual variation in the lasting effects of the social adversity. Such a feature might involve epigenetics or endocrine effects. Apparently comparable experiences have a sensitizing effect in some individuals, a steeling effect in others, and no discernable effect in yet others (38, 39). The limited available evidence suggests that a protective steeling effect is more likely following the experience of mild transient stressors, whereas a sensitizing effect tends to follow chronic adversities (39). If the biological feature truly reflects the environmental effect, it should differentiate between those, but does it? Second, some environmental effects persist over time, whereas others fade as time passes. Does the biological feature differentiate between these? Third, some effects vary with the person's age or sex. Is this variation reflected in the biological response?

All forms of social adversity tend to be multifaceted, making it essential to identify the key element that created the main risk for an adverse health outcome, and therefore the environmental element to investigate for its biological embedding. That is most difficult to determine with respect to social disadvantage (40), both because so many possibilities exist and because the key elements are likely to differ across the age span. Thus, in adulthood, personal lifestyle features, such as smoking, alcohol consumption, obesity, lack of exercise, and poor dietary balance, stand out (41). In the psychological arena, lack of control at work has been shown to be a key factor (42). In childhood, the main age period under consideration here, none of these are likely to be key. On the other hand, maternal smoking during the pregnancy, poor gestational growth, and fetal alcohol effects may exert important influences, particularly during the early years of childhood. Also, adverse experiences in early childhood may carry risk effects for coronary

artery disease in adult life before the age of 50 y, effects that must be mediated by some form of biological embedding (43, 44).

There has been surprisingly little research into these issues, but there have been some important findings. Thus, two studies using different samples and different designs (one experimental and one naturalistic) have compared the health prediction strengths of objective measures of social status (e.g., education, occupation) with subjective self-assessments (45, 46). It might be supposed that the objective measure is to be preferred, but both studies showed a superior predictive power of the subjective measure. The implication is that perceived status matters more than objective status. Interestingly, another study (47) found that subjective but not objective social status was associated with reduced gray matter volume, implying that self-perceived social standing is biologically embedded. Bulik et al.'s study (48) of the psychopathological consequences of sexual abuse of girls similarly depended on the meaning of the event rather than the severity of the physical act. As Adler and Rehkopf (40) emphasized, a range of natural experiment designs can be very helpful in pinning down the key risk element. A naturalistic prospective study (49) found very marked social differentials in the preschool years for both cognitive performance and socioemotional difficulties. However, the psychosocial environment appeared to explain more of the social variance statistically in behavioral outcomes than in cognitive ones. It remains uncertain whether this is a function of social status differences in neural processing (50).

In summary, social adversities are both heterogeneous in type and multifaceted. The key elements are likely to vary with age, and self-perceived social status may be more influential than objectively measured social standing. Similarly, the meaning of adverse experiences may be more important than their physical severity.

Possible Mediators of the Biological Embedding

Epigenetics. A wide range of possible mediators have been proposed. The term "epigenetics" is applied to mechanisms that change genetic effects (through influences on gene expression) without altering the gene sequence (51). It constitutes a major focus at the moment (52). There are several reasons for this interest. First, it appears to constitute a mechanism that has been conserved across a diverse range of organisms spanning birds, fish, rodents, and both human and nonhuman primates, as multiple papers in the special issue of PNAS show. Second, epigenetic changes are evident in relation to a great range of experiences. Third, such changes show the interesting mixture of considerable stability over time and yet responsivity to change. Fourth, the changes work through genetic influences, thus bringing it into the domain bridging nature and nurture. Fifth, it carries the potential of persistence across the generations. Finally, and most crucially, it has been subject to a rigorous and searching testing of the causal inference. For example, Meaney, Champagne, Weaver, and their colleagues (53–55), in their investigation of licking and archback nursing of rat pups used a cross-fostering design to determine whether the effects truly reflected environmental mediation; the findings showed that they did. The connection with a particular genetic location was shown, and the mediation was tested through reversal of methylation effects as a result of chemical treatment.

The functional importance of epigenetic effects [beyond the hypothalamic-pituitary-adrenal (HPA) axis effects shown by the Meaney group (54, 55)] was also shown by the role of epigenetics in genomic imprinting (such that the effects of genes vary according to whether the inheritance is through the mother or father) (56).

It is known that epigenetics is both tissue-specific and developmental phase-specific, making its investigation in living humans problematic [although it has been studied to good effect postmortem (57, 58) and there have been attempts to use buccal cells during life (59)]. Current animal model research is testing whether the study of lymphocytes constitutes a reasonable proxy for what is going on in the brain (it might do so because of the high level of expression in the brain compared with other tissues). Nevertheless, it cannot be assumed that the findings in different cell types will be identical.

Supposing that these methodological challenges can be successfully met, a range of substantive challenges will remain (60). The very pervasiveness of epigenetic changes as a result of experiences raises the query of whether mean differences between groups can result in meaningful differences among individuals within each group [an issue that bedevils the whole field of biomarkers (61)]. In other words, can the findings distinguish between the effects of different types of adversity or within the same adversity between individuals who show resilience and those who succumb? Supposing that mental (or physical) health outcomes reflect HPA axis effects brought about by epigenetic change, are such outcomes predicted better at the HPA level or the epigenetic level? Similar questions apply to other possibilities.

Neural Structure and Function. The investigation of institutional deprivation (62) provides the clearest example of the effects of profound social adversity on neural structure and function. In the English and Romanian Adoptees study, it was found that institutional deprivation that lasted beyond the child's age of 6 mo was associated with a very marked reduction in head size, with MRI findings showing a strong association with brain size. This effect was found in those without significant subnutrition (as indexed by body weight), and although there was substantial later catch-up in head growth, growth remained impaired until at least the age of 15 y. Electroencephalography and evoked event-related potential measures, as used in the Bucharest study, similarly showed a marked reduction in brain activity (63), although this improved if children were placed in high-quality foster care before the age of 2 y (64). Numerous animal studies have shown that repeated stress causes remodeling of hippocampal circuitry, as evidenced by shortening of dendrites, loss of spine synapses, and suppression of neurogenesis (65). In addition, there is an opposite effect on the amygdala. Human studies are much more limited, as well as lacking experimental control; however, they too have been interpreted as showing neurotoxic stress-related mechanisms.

HPA Axis Effects. There is an extensive animal model literature that shows elevated glucocorticoid levels following acute stress experiences (66); this has been interpreted as an adaptive response related to the need for fight/flight reactions to threat. Conversely, prolonged repeated stress tends to lead to hypocortisolism: low early-morning levels of cortisol and a blunted HPA axis response to stressors. These animal models rest heavily on the lack or loss of expectable parental care; hence, they probably equate to neglect rather than physical or sexual abuse of humans (1, 67). Nevertheless, human studies indicate the high frequency with which children suffer both neglect and maltreatment. Fisher et al. (68) found that previously maltreated foster children tended to show this apparently dysfunctional pattern of low cortisol patterns on waking and small declines between morning and evening cortisol levels. This dysregulated pattern was particularly associated with placement changes in foster care but was substantially prevented by attachment-based caregiver interventions.

Inflammatory Processes. In two separate studies, Danese et al. (69, 70) found that maltreatment in childhood was associated with an increased risk for clinically relevant inflammation processes, as measured by a categorical measure of high-sensitivity C-reactive protein (CRP), together with a dimensional measure of CRP, fibrinogen, and white blood cells. The effect of maltreatment on inflammation held even after controlling for a range of possible confounding variables. Although maltreatment had a significant effect in the absence of depression in adult life, there was no

significant effect of depression in the absence of maltreatment. This is an important finding, but its precise meaning is uncertain in view of the fact that the greatest effect was seen in the small group of individuals with both maltreatment and depression. Other research (71) has shown the effects of stress on the immune system and on rates of infection.

In summary, there is a wide range of possible mediators for the biological embedding of experiences. These include epigenetic mechanisms, damage to neural structure and function, neuroendocrine effects, and inflammatory processes. In all cases, there are questions as to whether group differences can account for individual (within-group) differences.

Gene–Environment Interdependence

There is now substantial evidence from animal models, human experimental approaches, and epidemiological studies of the reality and importance of gene–environment interaction (GxE) as investigated with molecular genetic identification of individual genes and robust measures of the environment (72–75). GxE is most evident in relation to child maltreatment rather than acute life events because it affects depression in adult life (76), suggesting that the biological process operates over a long time span and not mainly in provoking the onset of some mental disorder (76). It has also been found that the GxE mainly operates in relation to chronic or recurrent depression, rather than the provoking of onset of a single acute episode (77). That immediately raises the question of how GxE is reflected in biological embedding. Several implications are evident. First, there is huge individual variation in response to all forms of adversity: social, psychological, and physical (39). Even with gross abuse/neglect, some individuals escape serious consequences and some even appear to have been strengthened by their adverse experiences. It would seem highly likely that such resilience should be reflected in the biological embedding of experiences (78, 79), but that has yet to be demonstrated at an individual difference level.

Second, the lack of any apparent effect of maltreatment in the presence of particular genetic variants does not necessarily mean that the children have been unaffected. That is because the GxE is rather outcome-specific, and there will certainly be many outcomes that are not considered. Third, it cannot be assumed that the genes involved in GxE concern only vulnerability to adverse environments; there is growing evidence that the effect often concerns susceptibility to both good and bad environments (80). That means that the children with the apparently "risky" gene may also be the ones most likely to respond well to positive interventions.

GxE is the variety of gene–environment interplay that has received the most attention, but there are two other varieties that have implications for the biological embedding of experiences. First, gene–environment correlation (rGE) (3, 81) means that the risk effects of some experiences may be genetically mediated in part, emphasizing the need to test whether the risk effects are truly environmentally mediated. In addition, however, rGE shows the importance of people's shaping and selecting of experiences and implies the role of the active processing of experiences and not just their passive operation. Second, epigenetic effects mean that although environmental influences cannot change gene sequences, they can alter the effects of genes by changing gene expression (82). Genes can only have effects if they are expressed (72).

In summary, gene–environment interdependence is crucial to the bringing together of the range of causal processes that may be involved in the biological embedding of experiences.

Remaining Challenges

As the papers in the special issue of PNAS and the additional references used here well illustrate, there has been immense progress in studying the biology of environmental effects but considerable challenges remain. First, there needs to be much better conceptualization, categorization, and measurement of the several rather different forms of environmental adversity. Second, much greater use must be made of research strategies that can test environmentally mediated causal hypotheses. Third, there is a need to determine just what epigenetic changes do and do not account for. Put succinctly, do they explain individual differences in response to adversity and do they account for variations in health and behavior outcomes? Fourth, what do the findings on brain plasticity tell us about the neural responses to brain injury and environmental remediation? Fifth, what are the implications of GxE for an understanding of the effects of environmental influences and their biological embedding? Sixth, how can preventive interventions be better informed by the biological evidence?

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