

Enrich the environment to empower the brain

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Environmental enrichment (EE) has long been exploited to investigate the influence of the environment on brain structure and function. Robust morphological and functional effects elicited by EE at the neuronal level have been reported to be accompanied by improvements in cognitive performance. Recently, EE has been shown to accelerate the development of the visual system and to enhance visual-cortex plasticity in adulthood. These new findings highlight the potential of EE as a promising non-invasive strategy to ameliorate deficits in the maturation of the nervous system and to promote recovery of normal sensory functions in pathological conditions affecting the adult brain.

Nature and nurture in brain development

The old debate on the relative contribution of nature versus nurture to the construction and maintenance of brain architecture has led to the widely accepted consensus that genes and environment work in concert in shaping neural circuits and behaviour (for review, see Ref. [1]). Although the contribution of genetic program to development has been characterized and accepted early on in the debate, the role of the environment has remained vague for a long time, mostly because of the difficulties in quantifying environment-induced changes in the brain. It is only from the early 1960s that brain development ceased to be considered as an entirely experience-independent process.

On one hand, the classic experiments by Hubel and Wiesel [2] showed how dramatically early sensory deprivation can affect the anatomy and physiology of the visual cortex. These authors reported that occluding one eye (monocular deprivation, MD) early in development led to a severe reduction in the number of visual cortical cells responding to that eye, with a very strong increment in the number of neurons activated by the open eye. The same manipulation of visual experience turned out to be totally ineffective in the adult, and this period in early life characterized by enhanced plasticity in response to experience has become a classic example of critical period (CP). Consequently, the visual system started to be considered a prime model for studies on experience-dependent development and plasticity of the brain (for reviews, see Refs [3,4]).

On the other hand, fundamental contributions to the development of the nature–nurture debate came from the experiments by Rosenzweig and colleagues [5,6],

which introduced environmental enrichment (EE) as an experimental protocol specifically devoted to investigate the influence of environment on brain and behaviour, showing that the morphology, chemistry and physiology of the brain can be remarkably altered by modifying the quality and intensity of environmental stimulation. Since then, many studies have shown that EE elicits in the brain changes ranging from the molecular to the anatomical and functional level (for reviews, see Refs [7,8]).

These two highly fruitful fields (namely, visual-cortical plasticity and EE) have remained for a long time separated; recently, they have been combined together in a novel approach to investigate the effects of enhanced sensory-motor stimulation on the processes governing experience-dependent plasticity in the visual system. In this approach, the visual system has served as a model to study the effects of environment, leading to the discovery of previously unknown dramatic effects exerted by EE on the development and plasticity of neural circuits. At the same time, EE has emerged as a powerful tool to probe visual-circuit plasticity and to unravel the underlying molecular factors.

EE: definition and effects on brain and behaviour

The classic definition of EE is ‘a combination of complex inanimate and social stimulation’ [9]. Enriched animals are reared in large groups and maintained in wide stimulating environments where a variety of objects (e.g. toys, tunnels, nesting material and stairs) are present and change frequently. An essential component of a typical EE setting is the opportunity to attain high levels of voluntary physical activity on running wheels. Therefore, living in an enriched environment provides the animals with optimal conditions for enhanced exploration, cognitive activity, social interaction and physical exercise.

It is usually assumed that EE is simply a way of rearing the animals in a setting more similar to the wildlife: a kind of semi-naturalistic condition. However, the observation of rodents playing in an enriched environment, choosing when and how much to run on the wheel and to explore the new objects indicates the different idea that EE is not just a way to reproduce more natural life conditions. Rather, EE implies a kind of challenge-free interaction with a stimulating surrounding. We might speculate that, although the activity of mice and rats in the wild is mostly driven by necessity, in an EE it is usually prompted by a combination of curiosity and play.

EE has a variety of effects on the brain, which have been documented in several species of mammals from mice and rats up to cats and monkeys.

The first EE effects have been shown at the anatomical level, with EE determining robust increases in cortical thickness and weight [10,11], size of the cell soma and nucleus, dendritic arborisation, length of dendritic spines [12–14] and synaptic size and number [15–17]. More recent studies have shown that exposure to EE increases hippocampal neurogenesis [18] and reduces apoptotic cell death [19]. Exposure to EE has remarkably beneficial effects in animal models of nervous system disorders, including neurodegenerative diseases [20–22] and different types of brain injury [23–25].

One of the most amazing properties of EE is the capacity to modify behaviour, especially in tasks involving complex cognitive functions. EE enhances learning and memory [8,26,27] and reduces the cognitive decline typically associated with aging [8,26].

Investigation of the molecular mechanisms underlying EE influence on behaviour has the promising goal to find molecules that might be exploited to reproduce the beneficial effects of the enriched experience (the so called ‘enviromimetics’). First studies by Rosenzweig *et al.* [28] reported an increase in acetylcholinesterase activity, indicating an effect on the cholinergic system. Subsequent research confirmed and extended this initial observation to other neurotransmitter systems that have diffuse projections to the entire brain, such as the serotonergic [29] and the noradrenergic systems [30]. A large number of genes (several dozen) change their expression levels in response to EE, most of them in functional classes linked to neuronal structure, synaptic transmission and plasticity, neuronal excitability and neuroprotection [31,32]. One group of molecules particularly sensitive to environmental stimuli are neurotrophins [33], a class of secreted factors strongly implicated in structural and functional plasticity during development and in the adult [34]. Another factor crucial for EE neuroprotective effects is the insulin-like growth factor I (IGF-I) [24,35].