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Review

Inoculation stress hypothesis of environmental enrichment

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ABSTRACT

One hallmark of psychiatric conditions is the vast continuum of individual differences in susceptibility vs. resilience resulting from the interaction of genetic and environmental factors. The environmental enrichment paradigm is an animal model that is useful for studying a range of psychiatric conditions, including protective phenotypes in addiction and depression models. The major question is how environmental enrichment, a non-drug and non-surgical manipulation, can produce such robust individual differences in such a wide range of behaviors. This paper draws from a variety of published sources to outline a coherent hypothesis of inoculation stress as a factor producing the protective enrichment phenotypes. The basic tenet suggests that chronic mild stress from living in a complex environment and interacting non-aggressively with conspecifics can inoculate enriched rats against subsequent stressors and/or drugs of abuse. This paper reviews the enrichment phenotypes, mulls the fundamental nature of environmental enrichment vs. isolation, discusses the most appropriate control for environmental enrichment, and challenges the idea that cortisol/corticosterone equals stress. The intent of the inoculation stress hypothesis of environmental enrichment is to provide a scaffold with which to build testable hypotheses for the elucidation of the molecular mechanisms underlying these protective phenotypes and thus provide new therapeutic targets to treat psychiatric/neurological conditions.

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1. A history of environmental enrichment research

The "nature vs. nurture" debate began in earnest during the Victorian period, championed by Sir Francis Galton, who was inspired by the works of his cousin Charles Darwin. At issue was whether a person's expressed traits are a product of heritability (i.e. nature) or by his/her own experiences (nurture). Galton, bolstered by Darwin's theories on heritability came down firmly on the side of "nature". The opposing "nurture" side of the debate was best defined centuries before by John Locke's borrowed term "tabula rasa" (i.e. blank slate). The "nurture" side of the argument was further strengthened in the early 1900s by John Watson's theories on behaviorism.

As science evolved (particularly the advent of genetics), the "nature vs. nurture" debate evolved into a "genes vs. environment" debate, respectively. The battle raged on as scientists on both sides of the argument produced irrefutable evidence for their view. Eventually, scientists realized that both arguments were correct— that a person's expressed phenotype was due to an interaction of genes with environment. Thus, the Gene/Environment Interaction Theory was born. In a basic sense, the environment controls (to some degree) how genes are expressed. Thus, gene transcription is where the proverbial "rubber hits the road" and seems to play a significant role in the protective phenotypes produced by environmental enrichment (Green et al., 2010; Lobo et al., 2013; Zhang et al., 2014), which are described below in the beneficial effects of environmental enrichment.

The beginning of modern environmental enrichment research is mostly attributed to Rosenzweig, Renner, Bennett, Diamond and colleagues. This group used the environmental enrichment paradigm to show convincingly that the adult brain still exhibits plasticity and that, just like muscles, brains get stronger with greater use. Rats reared in an enriched condition (EC) have a thicker cortex, more dendritic arborization and greater cognitive abilities than rats reared in an isolated condition (IC) (Diamond et al., 1964; Renner and Rosenzweig, 1987; Rosenzweig and Bennett, 1996). Following these early experiments, many others have used environmental enrichment and found it to be a useful animal model in a variety of fields, particularly because it is a non-drug and non-surgical manipulation.

In parallel with Rosenzweig and colleagues, Harry Harlow was finalizing the ideas for his seminal work on the importance of maternal and social enrichment in rhesus monkeys (Harlow, 1958). Harlow designed inanimate wire and cloth "surrogate" mothers to show that maternal contact is enriching to baby macaques beyond merely providing food. Although Harlow's early work was oriented to the positive effects of maternal enrichment (i.e. affection), his later work shifted perspective to focus on the isolation aspect (i.e. lack of enrichment) rather than the enrichment itself (Harlow and Suomi, 1971).

2. What is environmental enrichment?

Environmental enrichment is complex and there are numerous ways to provide enrichment. There is a lack of consistency in protocols for enrichment between different laboratories, but the most common procedure in rats involves rearing the subjects in a large cage with novel objects and social contact with conspecifics for at least 30 days beginning immediately after weaning. The objects are replaced and rearranged daily to maximize novelty. This arrangement provides three key facets of enrichment: novelty, social contact and exercise. It has been shown in rats that all three aspects are rewarding (Bardo and Bevins, 2000; Belke, 2000; Bevins and Bardo, 1999) and all three release dopamine in the nucleus accumbens (Greenwood et al., 2011; Louilot et al., 1986; Rebec et al., 1997). Thus, it can be said that environmental enrichment is a compound manipulation that provides a daily workout for the dopamine system. Indeed, when the novel objects are replaced each day, the rats display a burst of exploratory activity lasting approximately 30 min that is beyond anything seen with locomotor stimulants like cocaine or amphetamine. Additionally, there is a second burst of exploratory/play behavior that occurs at the onset of the dark cycle, the beginning of the rats' normal period of high activity.

Although environmental conditions have a dramatic impact on the behavior of animals, these differing protocols for enriching rats often produce conflicting results. Parameters such as age of the animal, degree of enrichment, duration of enrichment, species and sex can each affect the results of an experiment. The lack of consistency in protocols likely stems from a lack of consensus regarding the definition of what indeed constitutes "environmental enrichment". Some might define enrichment based on environmental complexity—that a more complex environment is more enriching; however, environmental complexity alone is not the whole story. Environmental enrichment, by most definitions, should exert a positive influence on the organism, setting enrichment apart from overtly stressful events that have a negative impact on the organism. Thus, enrichment must provide an overall benefit to the organism. Further confusion in the field also arises from the fact that some researchers compare EC rats only to pair-housed social condition (SC) rats or compare only IC with SC rats (see below for discussion of the appropriate control for enrichment). However, without discounting or dismissing the views of others studying environmental enrichment using different protocols, this paper outlines a theory that the mild daily stresses of the enriched lifestyle are adaptive and inoculate rats to produce protective preclinical phenotypes for addiction and depression.

2.1. What are the beneficial effects of environmental enrichment?

As mentioned above, environmental enrichment contains three basic components: novelty, exercise and social contact. Animals are group-housed in a large cage equipped with children's plastic toys, which are replaced and rearranged every day. In order to study the "preventive" effect of environmental enrichment, rats are usually raised in the enriched condition before exposure to drugs (in the case of addiction research) or stress (in the case of depression research). Environmental enrichment attenuates the reinforcing effects of addictive drugs and produces an antidepressant-like effect (Brenes et al., 2008; Brenes Saenz et al., 2006; Green et al., 2010; Laviola et al., 2008). In addition, environmental enrichment can be studied as a "treatment" model, in which rats are assigned