Behavioural Brain Research 302 (2016) 81–87

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Early exposure to dynamic environments alters patterns of motor exploration throughout the lifespan

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HIGHLIGHTS

- Early rearing of mice in enriched environments improves motor flexibility later in life.
- This effect is most pronounced when the enriched environment changes daily.
- Opportunities for exercise or socialization do not have the same long-term impact.
- A dynamic environment produces region-specific changes in forebrain GLT1 expression.

ARTICLE INFO

Article history:
Received 20 July 2015
Received in revised form 1 December 2015
Accepted 5 January 2016
Available online 8 January 2016

Keywords:
Enriched environment
Isolated housing
Plus maze
Turning behavior
GLT1 expression

ABSTRACT

We assessed early rearing conditions on aging-related changes in mouse behavior. Two isolated-housing groups, running wheel (IHRW) and empty cage (IHEC), were compared against two enriched environments, static (EEST) and dynamic (EEDY), both of which included toys and other mice. For EEDY, the location of toys and sources of food and water changed daily, but remained constant for EEST. All mice, randomly assigned to one of the four groups at ~4 weeks of age, remained in their respective environments for 25 weeks followed by single housing in empty cages. Beginning at ~40 weeks of age, all mice were tested at monthly intervals in a plus-shaped maze in which we measured the number of arm entries and the probability of entering a perpendicular arm. Despite making significantly more arm entries than any other group, IHEC mice also were less likely to turn into the left or right arm, a sign of motor inflexibility. Both EEDY and EEST mice showed enhanced turning relative to IHRW and IHEC groups, but only EEDY mice maintained their turning performance for up to ~100 weeks of age. EEDY and EEST mice also were unique in showing an increase in expression of the major glutamate transporter (GLT1) in striatum, but a decrease in motor cortex, suggesting a need for further assessment of environmental manipulations on long-term changes in forebrain glutamate transmission. Our behavioral results indicate that early exposure to continually changing environments, rather than socialization or exercise alone, results in life-long changes in patterns of motor exploration.

1. Introduction

Mobility has been consistently shown to be an important marker of central nervous system function [1]. Declines in spontaneous motor behavior with advancing age have been observed in virtually every species examined, including *Caenorhabditis elegans*, mice, and humans (see Ref. [2] for a review). In particular, motor performance decreases as complexity of a given movement increases. In a mouse model of Huntington's disease (HD), an inherited but also an age-related condition [3,4], we found a decreased likelihood of performing a 90° turn into a perpendicular arm of a standard plus maze [5,6]. In healthy animals, moreover, turning was associated with anticipatory electrophysiological signaling in motor cortex and striatum, suggesting that this spontaneous motor response is an indicator of underlying brain function.

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http://dx.doi.org/10.1016/j.bbr.2016.01.007
0166-4328/

The benefits of environmental enrichment on healthy brain aging and motor performance have been widely observed and consistently replicated [7–11]. In fact, whereas aging impairs cortical and hippocampal circuitry [12], environmental enrichment promotes neurogenesis [13,14] and strengthens synaptic connections [7]. Socialization and exercise have long been considered critical components of this effect. But novelty also could be a major contributor. In fact, exposure to novelty increases the release of forebrain dopamine [15], and a dynamic environment, which includes novel experiences, aids in the maintenance of dopamine transmission and leads to healthy brain aging overall [16,17].

Here, we compared the effects of environmental novelty on aging-related turning behavior in mice previously housed in one of four environmental conditions for 25 weeks beginning shortly after weaning. Two groups lived in isolated housing—running wheel (IHRW) and empty cage (IHEC) – and two in enriched environments—static (EEST) and dynamic (EEDY). Both enriched groups included other mice and the same assortment of toys and sources of food and water, but only EEDY mice had these items changed every day, introducing a daily dose of novelty.

Another aspect of environmental enrichment is its ability to create reserve capacity or promote brain plasticity. The hypotheses of brain [18] and cognitive [19] reserves posit that behavioral and lifestyle patterns (e.g., higher educational attainment) in early adulthood play a strong role in healthy aging. Such reserves are built up and maintained against the effects of aging, leading to better brain health and behavioral outcomes in old age. Supporting the reserve hypothesis, rats raised in an enriched environment have been shown to be less vulnerable than standard-housed rats to brain insults that impair cognitive and motor function [20]. The aforementioned study, however, only tested the acute effects of enrichment in middle-aged animals (110 days-old), and did not test whether the reserve could be maintained even when all animals were returned to isolated housing. Thus, we assessed plus-maze turning long after environmental stimulation was withdrawn to determine the persistence of the behavioral change. Presumably, environmental enrichment early in the lifespan confers a level of plasticity that resists the effects of aging, even after enrichment has been withdrawn. Our experiment tests this hypothesis.

Improved turning performance in HD mice has been linked to increased uptake of glutamate in striatum mediated by increased expression of glutamate transporter 1 (GLT1) [21], the protein responsible for clearing >90% of this excitatory amino acid from striatal extracellular fluid [22]. Glutamate drives key aspects of neuroplasticity, including age- and environment-related changes in synaptic efficacy underlying learning and motor control [16,23–26]. By modulating the temporal profile of glutamate-induced changes in neuronal excitability, synaptic transmission, and other cellular functions [27], GLT1 is a likely major player in the neuroplastic changes underlying environmental enrichment. Interestingly, GLT1 expression declines with age [28,29], suggesting a potential involvement of GLT1 in any persistent aging-related changes in plus-maze turning induced by early exposure to our environmental manipulations. Thus, upon completion of behavioral testing, all groups were examined for GLT1 expression in striatum and in motor cortex, which not only supplies striatum with glutamate but also receives substantial glutamate input.

2. Methods

2.1. Subjects and groups

Male C57BL/6 mice used for this study were bred in the departmental animal colony at Indiana University Bloomington, which allowed unlimited access to food and water on a 12-h light–dark cycle (lights on at 07:30). All aspects of breeding and housing were approved by the institutional animal care and use committee, and followed National Institutes of Health guidelines. Mice were randomly assigned to one of the following four groups soon after weaning (~4 weeks of age) and remained in their respective environments for the next 25 weeks (see Fig. 1).

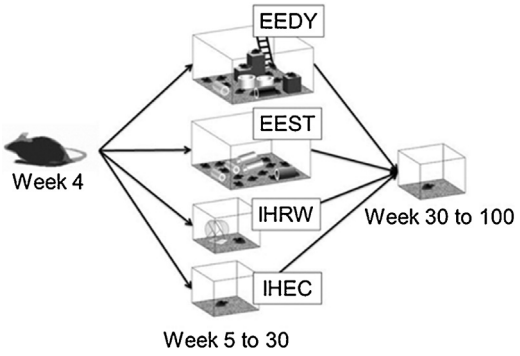

Fig. 1. Diagrammatic summary of the experimental conditions and timeline. See text for details.

2.1.1. IHEC—isolated housing: empty cage

This group served as the control condition. Mice were housed in isolation in standard clear-plastic cages (27 cm *L* × 17 cm *W* × 13 cm *H*) with a layer of inert bedding material.

2.1.2. IHRW—isolated housing: running wheel

This group served as the "exercise" condition. Mice were housed in isolation in clear-plastic cages (26 cm *L* × 20 cm *W* × 14 cm *H*) that could accommodate a plasticized running wheel (11 cm diameter) to permit bouts of spontaneous exercise. Wheel turns were monitored by computer to ensure that the wheel was active and each mouse used it on a daily basis.

2.1.3. EEST—enriched environment: static

This group served as the "exercise + socialization" condition. Mice were housed 12 to a cage (91 cm *L* × 43 cm *W* × 41 cm *H*), which was constructed of stainless steel mesh and rested on an oversize stainless steel tray filled with inert bedding material. Bedding was changed weekly by lifting the cage and lowering it onto a new tray with fresh bedding to minimize animal handling. The cage was filled with hard plastic and ceramic toys that provided opportunities for exploring, climbing, running, and escaping. The environment was kept "static" by maintaining the position of the toys as well as food and water sources during the entire 25-week period.

2.1.4. EEDY—enriched environment: dynamic

This group served as the "exercise + socialization + novelty" condition. Mice were housed 12 to a cage, which was serviced and provided with toys as described for EEST mice. To introduce novelty, the toys as well as food and water sources were repositioned daily, and new toys were inserted weekly.

After the 25-week experimental housing period, all mice were moved into isolated housing where they remained for the duration of the experiment. Beginning at ~40 weeks of age, mice were tested for plus-maze turning performance at monthly intervals for one year or longer.

2.2. Plus-maze testing

To measure spontaneous motor performance, mice were placed in a standard plus maze for 30 min while their movements were