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Different types of environmental enrichment have discrepant effects on spatial memory and synaptophysin levels in female mice

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Abstract

Environmental enrichment paradigms that incorporate cognitive stimulation, exercise, and motor learning benefit memory and synaptic plasticity across the rodent lifespan. However, the contribution each individual element of the enriched environment makes to enhancing memory and synaptic plasticity has yet to be delineated. Therefore, the current study tested the effects of three of these elements on memory and synaptic protein levels. Young female C57BL/6 mice were given 3 h of daily exposure to either rodent toys (cognitive stimulation) or running wheels (exercise), or daily acrobatic training for 6 weeks prior to and throughout behavioral testing. Controls were group housed, but did not receive enrichment. Spatial working and reference memory were tested in a water-escape motivated radial arm maze. Levels of the presynaptic protein synaptophysin were then measured in frontoparietal cortex, hippocampus, striatum, and cerebellum. Exercise, but not cognitive stimulation or acrobat training, improved spatial working memory relative to controls, despite the fact that both exercise and cognitive stimulation increased synaptophysin levels in the neocortex and hippocampus. These data suggest that exercise alone is sufficient to improve working memory, and that enrichment-induced increases in synaptophysin levels may not be sufficient to improve working memory in young females. Spatial reference memory was unaffected by enrichment. Acrobat training had no effect on memory or synaptophysin levels, suggesting a minimal contribution of motor learning to the mnemonic and neuronal benefits of enrichment. These results provide the first evidence that different elements of the enriched environment have markedly distinct effects on spatial memory and synaptic alterations.

Keywords: Radial arm maze; Working memory; Reference memory; Mouse; Exercise; Motor skill learning

1. Introduction

In the past few decades, much attention has been focused on the ways in which the mammalian brain can change in response to environmental experience. One of the most influential paradigms used to demonstrate this phenomenon is environmental enrichment. Environmental enrichment typically involves exposing rodents to a variety of stimuli such as toys, tunnels, running wheels, and social interactions with other cagemates. Enriched animals are generally compared with isolated controls (who are individually housed without any social interaction) or social controls (who are group housed but are not exposed to any other enriching stimuli). Of interest to the study of learning and memory is the fact that environmental enrichment can produce a wide range of morphological changes in regions of the brain critical for learning and memory, such as the hippocampus and neocortex. For example, enrichment increases dendritic branching and spine number, synaptic contacts and neurotransmission, and neuron size in the rat neocortex (Diamond, 1967; Diamond, Krech, & Rosenzweig, 1964; Globus, Rosenzweig, Bennett, & Diamond, 1973; Green & Greenough, 1986; Greenough & Volkmar, 1973; Greenough, Volkmar, & Juraska, 1973; Greenough, West, & DeVoogd, 1978; Rosenzweig & Bennett, 1996).

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Environmental enrichment in rats and mice also enhances many aspects of hippocampal physiology such as long-term potentiation (LTP) (Duffy, Craddock, & Nguyen, 2001), neurogenesis (Kempermann, Kuhn, & Gage, 1997; Nilsson, Perfilieva, Johansson, Orwar, & Eriksson, 1999), neurotrophin levels (Ickes et al., 2000; Pham et al., 1999; Pham, Winblad, Granholm, & Mohammed, 2002), dendritic spine growth and branching (Green, Greenough, & Schlumpf, 1983; Rampon et al., 2000), synaptophysin levels (Frick & Fernandez, 2003; Nithianantharajah, Levis, & Murphy, 2004), and NGF mRNA and CREB gene expression (Torasdotter, Metsis, Henriksson, Winblad, & Mohammed, 1996, 1998; Williams et al., 2001).

Consistent with effects of enrichment on the hippocampus and neocortex, enriched rodents also exhibit enhanced learning and memory abilities relative to rodents housed in social or isolated control conditions. Although early studies focused on mnemonic effects of enrichment early in development (Greenough, Wood, & Madden, 1972), more recent studies have demonstrated that enrichment initiated in adulthood can significantly improve performance on several tests of spatial and non-spatial memory. For example, spatial reference memory in the Morris water maze is improved in adult rats (Nilsson et al., 1999) and mice (Kempermann et al., 1997; Williams et al., 2001) exposed to 1–3 months of complex enrichment (including toys, running wheels, and cagemates) in the home cage relative to isolated or social controls. We recently reported that spatial working memory in a water-escape motivated version of the radial arm maze is significantly improved in adult C57BL/6 mice by 3 h/day of complex enrichment for several months (Gresack & Frick, 2004). Others have also shown that non-spatial memories, such as object recognition, social recognition, and contextual fear conditioning are enhanced by complex enrichment in mice (Duffy et al., 2001; Rampon et al., 2000; Tang, Wang, Feng, Kyin, & Tsien, 2001). In aging rodents, enrichment provides similar mnemonic benefits. For instance, complex enrichment in middle-aged and aged rats and mice reduces age-related deficits in numerous types of learning and memory including spatial reference memory tested in the Morris water maze (Frick & Fernandez, 2003; Frick, Stearns, Pan, & Berger-Sweeney, 2003; Kempermann, Kuhn, & Gage, 1998). In aged female mice, this spatial memory improvement was associated with significant increases in levels of the presynaptic protein synaptophysin in the hippocampus and neocortex (Frick & Fernandez, 2003).

The enriched environment utilized in most rodent studies consists of a combination of complex social and sensorimotor stimuli such as bigger cages, numerous toys, tunnels, and running wheels. For this reason, the relevance of any single contributing factor, such as cognitive stimulation or exercise, cannot be easily ascertained, and it seems likely that an interaction between multiple factors is important to the mnemonic enhancement seen in enriched rodents. However, some evidence suggests that single factors, such as voluntary exercise, can affect the brain in a similar manner as complex enrichment, with changes including enhanced hippocampal LTP (Kim et al., 2004) and neurogenesis (van Praag, Christie, Sejnowski, & Gage, 1999a; van Praag, Kempermann, & Gage, 1999b), increased hippocampal and neocortical neurotrophin mRNA expression (Neeper, Gomez-Pinilla, Choi, & Cotman, 1995, 1996), and reduced age-related hippocampal synaptophysin decline (Chen, Chen, Lei, & Wang, 1998). Exercise also improves spatial memory and preserves cognitive function during aging in both rats (Anderson et al., 2000; Fordyce & Farrar, 1991) and mice (Fordyce & Wehner, 1993b; van Praag et al., 1999a). Furthermore, work in humans indicates that physical fitness can enhance cognitive and memory functions (Clarkson-Smith & Hartley, 1989; Dustman et al., 1990; Lupinacci, Rikli, Jones, & Ross, 1993), and that long-term aerobic training may prevent age-related decline in cognitive function (Hill, Storandt, & Malley, 1993; Rogers, Meyer, & Mortel, 1990; Yaffe, Barnes, Nevitt, Lui, & Covinsky, 2001).

Other studies have focused on motor learning associated with acrobatic training, as opposed to repeated physical exercise, as a single enriching variable. Acrobatic training consists of repeated trials through a course designed to encourage problem solving and coordination. For instance, animals may need to learn to traverse various bridges (made of such items as chains, ropes, and wires) and obstacles to reach a series of platforms. This type of motor learning (as opposed to the motor activity involved in voluntary or forced exercise) significantly increases synapse formation in the cerebellar cortex (Kleim et al., 1998; Kleim, Vij, Ballard, & Greenough, 1997), whereas repetitive physical exercise increases cerebellar blood vessel density (Black, Isaacs, Anderson, Alcantara, & Greenough, 1990), suggesting that individual elements of the enriched environment may have markedly different effects on specific components of neural plasticity. Acrobatic training in rats also enhances synaptogenesis in the motor cortex and motor coordination following lesions of the sensorimotor cortex (Jones, Chu, Grande, & Gregory, 1999). If the motor skills acquired during the course of more conventional enrichment procedures contribute to memory improvement, then acrobatic training alone may benefit memory. However, the effects of motor skill learning on memory have yet to be examined.

Although a few attempts have been made to test the importance of single enriching factors such as socialization (Lu et al., 2003; Rosenzweig, Bennett, Hebert, & Morimoto, 1978) and general activity (Bernstein, 1973), no comparison has been made between different elements of the enriched environment in the same study. It is possible that separate elements of environmental