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BRAIN RESEARCH

Research Report

Myelination of the corpus callosum in male and female rats following complex environment housing during adulthood

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ABSTRACT

Myelination is an important process in brain development, and delays or abnormalities in this process have been associated with a number of conditions including autism, developmental delay, attention deficit disorder, and schizophrenia. Myelination can be sensitive to developmental experience; however, although the adult brain remains highly plastic, it is unknown whether myelination continues to be sensitive to experience during adulthood. Male and female rats were socially housed until four months of age, at which time they were moved into either a complex or "enriched" environment (EC) or an isolated condition (IC). Although the area of the splenium (posterior 20% of the callosum, which contains axons from visual cortical neurons) increased by about 10% following two months of EC housing, the area occupied by myelinated axons was not influenced by adult housing condition. Instead, it was the area occupied by glial cell processes and unmyelinated axons which significantly increased following EC housing. Neither the size nor the myelin content of the genu (anterior 15% of the callosum) was sensitive to manipulations of adult housing condition, but males had more area occupied by myelinated axons in both callosal regions. Finally, the inability of two months of complex environment housing during adulthood to impact the number of myelinated axons in the splenium was confirmed in a subset of animals using quantitative electron microscopy. We conclude that the sensitivity of myelination to experience is reduced in adulthood relative to development in both sexes.

1. Introduction

The brain is exquisitely responsive to experience, including learning. Since Hebb and his students first showed that housing rats in a complex environment improves their performance on numerous tests of rodent cognition (Forgays and Forgays, 1952; Hebb, 1949; Hymovitch, 1952), this so-called "enrichment" paradigm has been a favorite of researchers interested in understanding how the brain reorganizes itself to accomplish learning. Raising animals in a complex environment induces dendritic growth and synaptogenesis on neurons in many neocortical areas (Greenough and Volkmar, 1973;

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Markham and Greenough, 2004; Turner and Greenough, 1983, 1985). While the most dramatic effects have been seen following developmental experience, similar changes in neuronal morphology have been reported following complex environment housing or training on a learning paradigm during adulthood (Black et al., 1990; Greenough et al., 1979; Greenough et al., 1985; Juraska et al., 1980; Kleim et al., 1996; Markham and Greenough, 2004; Uylings et al., 1978). For example, rats housed in a complex environment as adults for either 30 or 60 days had significantly more synapses per neuron in the visual cortex compared to control animals of the same age (Briones et al., 2004). Animals that had experienced the complex environment for 30 days and then were placed in individual housing for a subsequent 30 days were comparable to animals subjected to the reverse sequence, reflecting the persistence of experience-induced synaptic plasticity (Briones et al., 2004). Similarly, learning-induced changes in cerebellar synapse number persisted undiminished for at least four weeks after training on a motor learning task was completed (Kleim et al., 1997).

In recent years it has become clear that experience-driven structural changes in the brain are by no means limited to neurons. For example, the degree of synaptic ensheathement by astrocytic processes is increased by complex environment housing (Jones and Greenough, 1996), and enrichment induces increases in astrocytic cell size (hypertrophy) and number (hyperplasia) (Anderson et al., 1994; Jones and Greenough, 2002; Sirevaag and Greenough, 1987, 1991). In general, morphological plasticity of astrocytes in response to complex environment housing occurs on a time scale that is comparable to the timeline for neuronal changes that occur in this paradigm (Jones and Greenough, 1996; Jones et al., 1996; Sirevaag and Greenough, 1985). In contrast to neuronal changes, however, learning-induced astrocytic hypertrophy appears to be more transient (Kleim et al., 2007).

Evidence also suggests that oligodendrocytes are responsive to experience. In the visual cortex, increases in the density and volume fraction of oligodendrocyte nuclei have been observed following developmental rearing in a complex environment (Sirevaag and Greenough, 1987; Szeligo and Leblond, 1977). The influence of developmental experience on oligodendrocytes is not limited to the visual cortex; Juraska and Kopcik (1988) found that raising rats in a complex environment increased the number of myelinated axons in the splenium (the portion of the corpus callosum that contains visual cortical axons; Kim et al., 1996). A similar effect has also been demonstrated in rhesus monkeys—when raised in a complex environment, they have larger corpora callosa (Sanchez et al., 1998). Finally, in humans, extensive piano practicing beginning during childhood increases fractional anisotropy, a measure thought to be correlated with degree of myelination (Larvaron et al., 2007), in cerebral white matter (Bengtsson et al., 2005).

Despite studies indicating that myelination continues well into adulthood in both rodents and humans (Benes et al., 1994; Nunez et al., 2000; Yakovlev, 1967; Yates and Juraska, 2007), the question of whether myelination remains sensitive to experience during adulthood has remained largely unexplored. The conversion of previously unmyelinated axons to the myelinated fiber pool could be a form of plasticity with a potential comparable to the addition or strengthening of synapses, with speed rather than efficacy of communication being enhanced in this case: myelinated axons conduct action potentials at velocities that are ~50–100 times faster than unmyelinated axons (Brinley, 1980).

The present experiment was designed to determine whether myelination is responsive to experience in adulthood, using the complex housing environment paradigm (see Fig. 1 for experimental design). Animals were housed in small groups until adulthood, at which time half of the animals were moved into a complex environment ("enriched condition" or EC) and half were moved into a standard cage and housed alone ("isolated condition" or IC). After one month, half of the animals switched housing conditions, while the other half remained in their original condition for a second month, thus creating four groups of animals: IC/IC, IC/EC, EC/IC, and EC/EC (see experimental procedures for details). Comparison of IC/EC and EC/EC groups (i.e., one vs. two months of EC housing) was designed to indicate whether any identified effect of adult housing on myelination was additive, and comparison of EC/IC and IC/EC groups would indicate how well an effect of complex environment housing persisted in the absence of continued exposure to the environment. Both males and females in the various conditions were examined because sex differences occur in callosal myelination (Kim et al., 1996; Kim and Juraska, 1997; Mack et al., 1995) and can vary with rearing environment (Juraska and Kopcik, 1988).

2. Results

2.1. Callosal length

The total anterior to posterior length of the callosum was greater in males than females ($F_{1,49}=14.2$, $p<.0001$; males: 7.25 mm ± 0.03 mm, females: 7.06 mm ± 0.04 mm) and was influenced by housing ($F_{3,49}=3.2$, $p<.04$) (Fig. 2). The corpus callosum was longer in both groups of animals that were

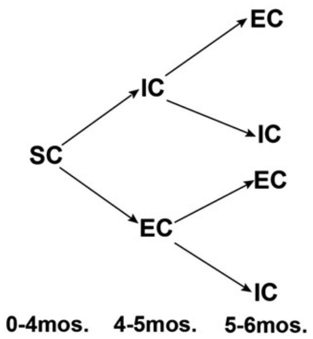

Fig. 1 – Experimental design. Animals were housed in small groups ("social condition" or SC) until age 4 months (adulthood), at which time half of the animals were moved into a complex environment ("enriched condition" or EC) and half were moved into a standard cage and housed alone ("isolated condition" or IC). After one month, half of the animals switched housing conditions, while the other half remained in their original condition. All animals were sacrificed at age 6 months.