

Please cite this article in press as: Hirase H, Shinohara Y. Transformation of cortical and hippocampal neural circuit by environmental enrichment. *Neuroscience* (2014), <http://dx.doi.org/10.1016/j.neuroscience.2014.09.031>

Neuroscience xxx (2014) xxx–xxx

NEUROSCIENCE FOREFRONT REVIEW

TRANSFORMATION OF CORTICAL AND HIPPOCAMPAL NEURAL CIRCUIT BY ENVIRONMENTAL ENRICHMENT

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Abstract—It has been half a century since brain volume enlargement was first reported in animals reared in an enriched environment (EE). As EE animals show improved memory task performance, exposure to EE has been a useful model system for studying the effects of experience on brain plasticity. We review EE-induced neural changes in the cerebral cortex and hippocampus focusing mainly on works published in the recent decade. The review is organized in three large domains of changes: anatomical, electrophysiological, and molecular changes. Finally, we discuss open issues and future outlook toward better understanding of EE-induced neural changes. © 2014 Published by Elsevier Ltd. on behalf of IBRO.

Key words: enriched environment, cerebral cortex, hippocampus, neuropil, spines, glia, gamma oscillations.

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Abbreviations: ACC, anterior cingulate cortex; AMPA, alpha-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid; BDNF, brain-derived neurotrophic factor; CaMKII, Ca²⁺/calmodulin-dependent protein kinase II; cAMP, cyclic adenosine monophosphate; CREB, cAMP-response element-binding protein; ECM, extracellular matrix; ECS, extracellular space; EE, enriched environment/environmental enrichment; ELISA, enzyme-linked immunosorbent assay; GABA, gamma-aminobutyric acid; GAD65, glutamate decarboxylase 65; GFAP, glial acidic fibrillary protein; GPCR, G-protein-coupled receptor; IGF-1, insulin-like growth factor-1; KO, knock out; LFP, local field potential; LTP, long-term potentiation; MD, monocular deprivation; MRI, magnetic resonance imaging; NGF, nerve growth factor; NMDA, N-methyl-D-aspartate; NMDA-R, NMDA receptor; NT-3, neurotrophin-3; PKC, protein kinase C; PSD, postsynaptic density; PV, parvalbumin; tPA, tissue-type plasminogen activator; SSRI, selective serotonin reuptake inhibitor; VIP, vasoactive intestinal peptide.

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INTRODUCTION

The plastic nature of the brain allows animals to change their behavior to adapt to their environment. Remarkably, a given animal's capacity for both plasticity and successful behavioral adaptation is greatly influenced by its postnatal experience. For example, animals nurtured in a housing condition with environmental enrichment (EE, enriched environment) develop enhanced memory and learning abilities compared with those with standard caging conditions (van Praag et al., 2000; Nithianantharajah and Hannan, 2006; Simpson and Kelly, 2011, for reviews). EE is achieved across three axes. First, EE contains a larger habitable area in which physical objects like toys, tunnels, and running wheels are placed to promote animals' sensory and motor experience. Second, these objects are changed regularly, so as to keep animals' curiosity and voluntary exploration high. Third, animals are housed in groups to promote social interactions. Animals are typically reared in EE for a few to several weeks, during which these components are thought to synergistically influence brain plasticity. Additionally to cognitive enhancement effects, EE rearing has gained growing attention in the recent decade as it has been shown to have resilient, mitigating and sometimes recuperating effects in various neurological conditions including Alzheimer's disease, Huntington's disease, Rett Syndrome, and stroke (Nithianantharajah and Hannan, 2006; Pang and Hannan, 2013, for reviews).

Past studies have demonstrated that EE induces visible structural and functional changes in the brain. Description of enlarged brain volume and increase of dendritic morphological complexity in the cerebral cortex

and hippocampus date back to 1960s (Bennett et al., 1964; Diamond et al., 1964) and detailed anatomical studies carried out in the following years confirmed these results. Another significant structural change is enhanced adult neurogenesis in the dentate gyrus of the hippocampus (Kempermann et al., 1997). While the contribution of neurogenesis to improved memory task performance remains controversial (Bruehl-Jungerman et al., 2005; Meshi et al., 2006; Kerr et al., 2010; Bednarek and Caroni, 2011; Akers et al., 2014), these newly generated cells certainly innervate their target cells thus reorganizing the neural circuit.

Molecular genetics and physiological recording techniques have progressed tremendously since the days EE-induced structural changes were first noticed. Almost every cell type can now be molecularly labeled and manipulated by clever combinations of transgenic mice and recombinant viruses. Moreover, the activity of these cells can be manipulated by optogenetics or pharmacogenetics. *In vivo* two-photon microscopy and high-density extracellular electrophysiology provide means to observe dynamic changes of neural structure and activity, respectively. With these methodological advancements, the next likely step to advance our knowledge on experience-dependent modification of brain capacity is to understand the neuropil dynamism caused by EE exposure. This review aims to discuss recent progress on the neuropil reorganization and associated molecular changes triggered by EE exposure during juvenility to adulthood.

RECENT VIEWS OF NEUROPIIL

The term “neuropil” traditionally refers to the commingled substrate consisting of axons, dendrites, and glial cells typically observed in the gray matter of the central nervous system (Fig. 1). Serial electron microscopic reconstruction of neuropil, particularly by use of block-face scanning electron microscopy, has made it

possible to efficiently quantify the composition of neuropil. For instance, Mishchenko et al. (2010) reported that in rat hippocampal CA1 stratum radiatum neuropil, axons and dendrites occupy nearly 50% and 40% of the volume, leaving 8% for glial processes and the rest for the extracellular space (ECS). It has been suggested that ECS fraction assessed by electron microscopy could be underestimated as cells swell during the fixation process (Van Harrevelde et al., 1965). In fact, other works by electron microscopy using rapid-freezing samples, *in vivo* iontophoretic or optical measurements estimated the ECS fraction to be 15–20% (reviewed in Sykova and Nicholson, 2008).

While the volume of axons and dendrites are comparable, individual axons are smaller in volume than dendritic processes. Intricate axonal innervation in the neuropil often results in several axons being within reach of a single dendritic spine (Stepanyants et al., 2002; Mishchenko et al., 2010). Of note, the average number of reachable axons from a spine is a few times higher in primates than in rodents, suggesting a higher degree of freedom for connectivity modification of the neural circuit (Escobar et al., 2008).

The majority of cortical and hippocampal synapses are excitatory asymmetrical synapses characterized by the presence of electron-dense postsynaptic density (PSD) in the electron micrograph. The PSD is packed with proteins for synaptic signal transduction, such as glutamate receptors, calcium/calmodulin-dependent kinase 2, actin, PSD95 and shank family proteins. The ratio of symmetrical and asymmetrical (i.e. inhibitory vs. excitatory) synapses is roughly 1/9 and is similar among mammalian species. The density of synapses are estimated to be $1.1/\mu\text{m}^3$ in human temporal cortex, $1.4/\mu\text{m}^3$ in rat hindlimb somatosensory cortex, $2.9/\mu\text{m}^3$ in mouse barrel cortex, and $2.5/\mu\text{m}^3$ in mouse visual cortex (DeFelipe et al., 2002). Mouse synapses are generally more compact than those of humans or rats, with the mean cross section length being about 75% of rat or

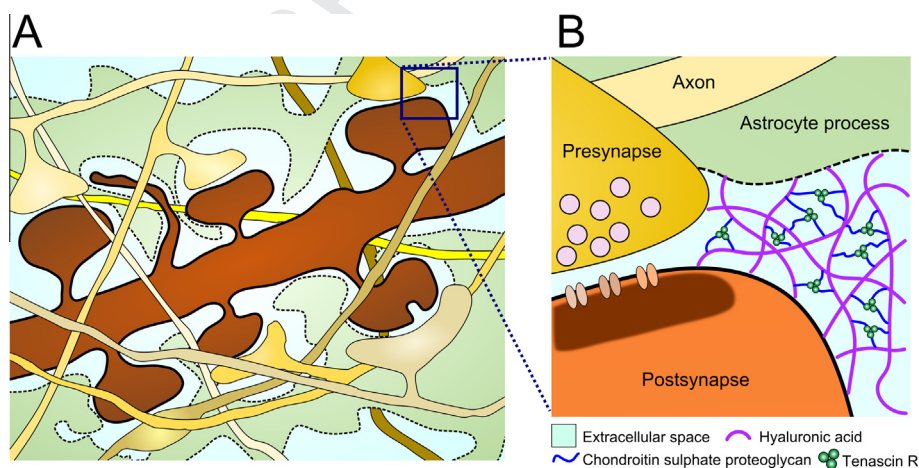


Fig. 1. A simplified representation of neuropil. (A) The main cellular constituents of neuropil are dendritic segments (brown object with thick outline – a dendritic branch with spines and a filopodia), axons (yellowish structures with thin outline), and surrounding astrocytic microprocesses (green structures with dashed outline). (B) In addition, the extracellular space (ECM, cyan background) and extracellular matrix, which consists of a meshed network organization consisting of hyaluronic acid, chondroitin sulfate proteoglycan, tenascin R, along with collagen and other glycoproteins such as laminin and fibronectin (not shown in this diagram).

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