Adult neurogenesis-dependent spatial learning and olfactory memory are enhanced by extremely low-frequency electromagnetic fields in mice

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Throughout life adult neurogenesis generates new functional neurons from neural stem cells (NSCs) mainly residing in two brain areas: the subgranular zone (SGZ) of the dentate gyrus (DG) in the hippocampus and the subventricolar zone (SVZ) lining the walls of the lateral ventricles within the forebrain. Substantial evidence supports critical roles of these adult-born neurons for specific brain functions, such as learning and memory. Moreover, impairment of adult neurogenesis characterizes brain aging and plays a role in age-related neurodegenerative disorders. Therefore, interventions able to improve the endogenous neurogenic capacity have a great potential therapeutic value.

We investigated the effects of *in vivo* exposure to extremely low-frequency electromagnetic fields (ELFEFs, 1mT, 50Hz) on both DG and SVZ neurogenic niches. Our findings unveiled positive effects of ELFEFs on both adult NSC sources (Piacentini et al., 2008; Cuccurazzu et al., 2010; Podda et al., 2014; Leone et al., 2014, 2015). In particular, we found that mice exposure to ELFEFs promoted proliferation, survival and neuronal differentiation of hippocampal NSCs that functionally integrated in the DG. The enhanced hippocampal neurogenesis induced by ELFEFs significantly improved synaptic plasticity and hippocampal-dependent learning and spatial memory. With regard to the underlying molecular mechanisms, we found that the ELFEF-induced increase in NSC proliferation and neuronal differentiation rely on epigenetic mechanisms regulating the expression of neurogenic genes, including Hes1, Neurogenin1 and NeuroD1.

Accordingly, we found that ELFEFs also significantly enhanced olfactory memory via increased adult neurogenesis in the SVZ. Specifically, mice exposed to ELFEFs exhibited increased odor discrimination and improved short- and long-term olfactory memory that were associated with enhanced adult neurogenesis in the SVZ and the olfactory bulb (OB). The improved olfactory learning and memory depended on Wnt3 signaling to increase nuclear localization of its downstream target β-catenin, and the expression of neurogenic genes. Indeed, inhibition of Wnt3 by Dkk-1 prevented the ELFEF-induced up-regulation of neurogenic genes and abolished ELFEF's effects on olfactory memory. These findings characterize a new molecular mechanism relying on the Wnt/β-catenin pathway, that regulates olfactory memory in mice and might be exploited in the future for the treatment of brain disorders associated with impaired adult OB neurogenesis and memory including mood-related disorders.

Collectively, our studies further underscore the potential of ELFEFs to boost neurogenesis and counteract functional alterations associated with normal aging or/and neurodegenerative diseases. Moreover, our study identifies two different but interconnected molecular mechanisms responsible for ELFEF-induced enhancement of hippocampal and OB neurogenesis, that could be targeted in future stem cell-based therapeutic approaches.