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Modulating Neuronal Competition Dynamics in the Dentate Gyrus to Rejuvenate Aging Memory Circuits

Highlights

- Mature DGC spine elimination enhances integration of adult-born DGCs
- Adult neurogenesis dictates population-based coding in the DG
- Integration of adult-born DGCs transiently reorganizes local afferent connectivity
- Rejuvenating the aged DG with adult-born DGCs promotes memory precision

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In Brief

McAvoy et al. demonstrate that neuronal competition dictates integration of adult-born dentate granule neurons. By biasing competition in favor of adult-born neurons in adulthood and aging, McAvoy et al. rejuvenate the dentate gyrus with new neurons and improve remapping and memory.

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Modulating Neuronal Competition Dynamics in the Dentate Gyrus to Rejuvenate Aging Memory Circuits

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SUMMARY

The neural circuit mechanisms underlying the integration and functions of adult-born dentate granule cell (DGCs) are poorly understood. Adult-born DGCs are thought to compete with mature DGCs for inputs to integrate. Transient genetic overexpression of a negative regulator of dendritic spines, Kruppel-like factor 9 (Klf9), in mature DGCs enhanced integration of adult-born DGCs and increased NSC activation. Reversal of *Klf9* overexpression in mature DGCs restored spines and activity and reset neuronal competition dynamics and NSC activation, leaving the DG modified by a functionally integrated, expanded cohort of age-matched adult-born DGCs. Spine elimination by inducible deletion of Rac1 in mature DGCs increased survival of adult-born DGCs without affecting proliferation or DGC activity. Enhanced integration of adult-born DGCs transiently reorganized adult-born DGC local afferent connectivity and promoted global remapping in the DG. Rejuvenation of the DG by enhancing integration of adult-born DGCs in adulthood, middle age, and aging enhanced memory precision.

INTRODUCTION

Neural stem cells (NSCs) in the dentate gyrus (DG) sub-region of the hippocampus generate dentate granule cells (DGCs) throughout life, with substantial turnover of the DG reported in humans (Altman and Das, 1965; Eriksson et al., 1998; Spalding et al., 2013). Considerable evidence suggests that levels of adult hippocampal neurogenesis are highly sensitive to experience (Kempermann et al., 1997; van Praag et al., 2000), indicating that neurogenesis is dynamically regulated by circuit demands. It has been suggested that adult-born DGCs must compete with mature DGCs for entorhinal cortical inputs in order to integrate into the hippocampal circuit. Anatomical studies show that maturing adult-born DGCs first form synapses onto pre-existing perforant path-DGC synapses, before establishing monosynaptic connections with those perforant path terminals (Toni et al., 2007). Deletion of the N-Methyl-D-aspartate (NMDA) receptor in 2- to 3-week-old adult-born DGCs impairs their survival, indicating a role for activity in integration of adult-born DGCs (Tashiro et al., 2006). These observations raise the possibility that mature DGC input connectivity dictates the dynamics of adult-born DGC competition.

Studies interrogating functional contributions of adult hippocampal neurogenesis support a role for adult-born DGCs in resolving interference between competing goals or overlapping contextual or spatial information (Wojtowicz et al., 2008; Clelland et al., 2009; Garthe et al., 2009; Tronel et al., 2012; Sahay et al., 2011a; Burghardt et al., 2012; Nakashiba et al., 2012; Niibori et al., 2012; Pan et al., 2012; Vukovic et al., 2013; Swan et al., 2014; Besnard and Sahay, 2016). Aging is accompanied by numerous changes in the hippocampus associated with impairments in resolution of interference (Toner et al., 2009; Yassa et al., 2011; Yassa and Stark, 2011; Gracian et al., 2013; Wu et al., 2015). Whether enhancing adult hippocampal neurogenesis in middle age or during aging improves memory functions is not known.