‘Selective engram co-reactivation in idling brain inspires implicit learning’

Summary of PhD thesis

A memory is represented by the activity of distinct neurons known as “engram cells”, which are stimulated during a learning experience and consolidated afterwards for future processing. Flexible updating of our past experiences with novel relevant encounters known as “assimilation”, is important for higher-order functions such as implicit learning, creativity, and insight. However, there is a lack of direct causal evidence for the utility of stored neural correlates in the interaction between memories to be formed and pre-existing ones, which this flexibility rationally entails. Moreover, previous work has suggested that the idling states like post-learning sleep could also inspire creative thinking. However, the nature, exclusivity, and necessity of the involved offline processing remain unknown. Here, we show that, parallel to the consolidation of a new experience in the mouse cortex, reactivations of pre-stored engram cells of a subtly related memory spontaneously emerge, leading to their assimilation by extracting their commonality during post-learning sleep. We established a paradigm using mice that links/separates context-dependent memories based on their geometrical similarities. Animals were exposed to one of four environments with different geometric conformations one day before undergoing contextual fear conditioning (CFC) in a square context. Mice showed gradual fear transfer to pre-exposed geometrically-relevant contexts next day, but not after 15 min. CFC memory consolidation rather than assimilation was disrupted upon interference with the post-CFC $GABA_A$ receptor-mediated activity of the prelimbic cortex (PL). However, both processes were impaired after similar perturbations in the Anterior Cingulate Cortex (ACC). *In vivo* calcium imaging revealed that neurons in the ACC representing relevant, rather than distinct, memories were significantly co-reactivated during post-CFC sleep, but not throughout CFC or post-CFC awake periods. Disrupting the ACC co-reactivations during post-CFC sleep by engram-specific optogenetic inhibition of the related memory prevented assimilation while preserving CFC memory consolidation. These results suggest that assimilating pertinent memories during sleep by co-reactivation of their respective engram cells in the ACC represents the neural underpinnings of sleep-triggered implicit learning and extraction of commonalities between life events to update our knowledge. Finally, distinct roles played by the $GABA_A$-mediated modulation of post-encoding activity of ACC and PL indicates the division of labour among cortical circuits, thereby permitting the separation of new experience processing and its assimilation to prior knowledge.

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