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Title: Inducible ablation of NCAM impairs preformed hippocampus- and cortex-dependent fear memories

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Authors: O. SENKOV<sup>1</sup>, \*A. E. DITYATEV<sup>2</sup>, T. MAKHINA<sup>2</sup>, G. DITYATEVA<sup>2</sup>, P. CHAMBON<sup>3</sup>, D. METZGER<sup>3</sup>, M. SCHACHNER<sup>2</sup>, A. K. ENGEL<sup>1</sup>;  
<sup>1</sup>Dept. of Neurophysiol. and Pathophysiology, <sup>2</sup>Ctr. Mol. Neurobiology, Univ. Med. Ctr. Hamburg-Eppendorf, Hamburg, Germany; <sup>3</sup>Physiological Genet. of Nuclear Signaling Depart, Inst. of Genet. and Mol. and Cell. Biol., Illkirch, France

The neural cell adhesion molecule NCAM is required for hippocampus-dependent synaptic plasticity and acquisition and consolidation of contextual fear memory (Senkov et al., 2006, J Neurosci 26: 10888-10898). However, the role of NCAM at later stages of hippocampal memory storage and retrieval and its importance for amygdala- and cortex-based fear memories are less clear. Here, we took an advantage of the Cre-estrogen-receptor-tamoxifen-triggered (Cre-ERT) recombinase transgenic system (Weber et al., 2001, Eur J Neurosci 14: 1777-1783), which allowed us to inducibly and acutely ablate NCAM expression in the adult brain and perform within-subject comparison of learning and memory before and after removal of NCAM at different stages of memory formation. We found that NCAM-floxed mice expressing Cre-ERT under control of the PrP promoter showed normal levels of NCAM and normal contextual memory on the 1<sup>st</sup> and 7<sup>th</sup> days after the first fear conditioning. However, after injection of tamoxifen for 5 consecutive days these mice exhibited a strong reduction in expression of NCAM and in contextual memory tested on the 14<sup>th</sup> and 21<sup>st</sup> days after the first fear conditioning, suggesting that acute NCAM removal weakens preformed memories or their retrieval. As controls, we used three different groups: vehicle-injected NCAM-floxed Cre-ERT expressing mice, or NCAM-floxed mice not expressing Cre-ERT, which were injected either with tamoxifen or vehicle. No difference between control groups was found in fear conditioning. When NCAM-floxed Cre-ERT expressing mice were repetitively conditioned (using a context and tone distinct from those used in the first fear conditioning) after induced ablation of NCAM, they showed a robust deficit in formation of contextual memory on the 1<sup>st</sup> and 7<sup>th</sup> test days. Retrieval and formation of amygdala-dependent tone memory was, however, undisturbed after inducible NCAM removal. NCAM constitutive knockout mice injected with vehicle and tested in the same manner as NCAM-floxed mice showed sustained impairment in contextual and tone memory after the first and second fear conditioning. When NCAM was ablated 30 days posttraining, at the time when hippocampus-dependent memory is transferred into anterior cingulate cortex-dependent state (Frankland et al., 2004, Science 304: 881-883), the mice showed robust deficit in contextual memory but not in tone memory. Thus, our data suggest that acute ablation of NCAM impairs formation and storage/retrieval of recent and remote contextual fear memories in the hippocampus and cortex, but does not affect amygdala-dependent cued memory.

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