TP13: Learning from mistakes: Cholinergic modulation of interactions between performance monitoring and long-term memory (Markus Ullsperger)

Performance monitoring (PM) improves memory encoding such that it prevents the encoding of false engrams and corrects engrams that turn out to be wrong. PM is an essential cognitive function that underlies the detection of performance problems and errors and the initiation of subsequent compensatory and adaptive mechanisms. In humans, the posterior medial frontal cortex (pMFC), particularly the anterior midcingulate cortex (aMCC) is a key structure representing PM signals, which indicate the need for adjustments (Ullsperger et al., 2014). Influential current theories suggest that PM builds on prediction errors serving as teaching signals which enable learning, but the interactions of PM and LTM encoding has not been studied extensively yet. Direct anatomical connections from the aMCC to the hippocampus via the cingulate bundle suggest close functional interactions. A small number of studies have reported functional interactions between activity in aMCC and the hippocampus (Hip) that appear to underlie learning from errors (Klein et al., 2007; Hester et al., 2008). Acetylcholine (ACh) plays a major role in cognitive functions such as long-term memory (LTM), attention, PM, and adaptive control (Dumas and Newhouse, 2011; Danielmeier et al., 2015), which have been shown to decline with increasing age. Whereas a reduction in ACh signaling (mainly due to neurodegeneration in the basal forebrain) has been shown to contribute to cognitive decline in pre-clinical and clinical Alzheimer's dementia, the course of ACh activity across healthy aging is less clear. It appears that ACh availability is an important factor that can at least partly compensate for cognitive decline resulting from other changes, e.g., cortical impairment at the synaptic level (Janeczek et al., 2017). Furthermore, it has been proposed that the ability of the cholinergic system to modulate cognitive performance depends on synaptic integrity (Dumas and Newhouse, 2011) (**Figure 14D**).

Hypothesis: PM, in particular processing of feedback, strengthens encoding of correct information in LTM and devalues engrams of remembered associations that turned out to be incorrect via interactions between pMFC and Hippocampus (Hip). Older people are less able to utilize feedback to correct memory engrams, i.e. make more repeated errors and increasing ACh transmission is expected to alleviate individual (age-related) deficits in learning from errors, whereas blocking ACh receptors can mimic such deficits in young participants. We define the following Aims:

We will establish a paradigm that allows (a) to study the interaction of two major cognitive functions declining with age, PM and LTM, (b) to investigate the systemic and cognitive effects of age-related changes in synaptic interactions, and (c) to determine the role of ACh and its ability to compensate cortical dysfunction. Specifically, we will:

1. investigate the mutual interactions of PM in pMFC and Hip-based LTM encoding.
2. investigate the role of ACh in these interactions, its changes with healthy aging, and its modulation by pharmacological intervention with clinically established pharmaceuticals affecting cholinergic transmission.
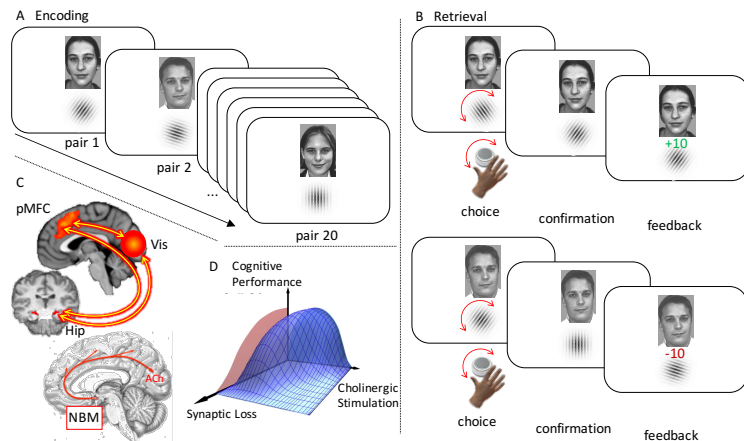
Behavioral task and hypotheses. (A) During encoding, participants learn pairs of unknown faces and tilted Gabor patches. **(B)** To test LTM, on each trial they are presented with a learned face and use a dial to indicate the tilt of the associated Gabor patch. Together with feedback (reward on correct responses, loss on errors), the correct tilt is re-displayed. Each face is tested three times in pseudorandom order. Analysis will compare repeated errors (no feedback effect on engram) with corrected errors (correct response on the 2nd or 3rd presentation of a face response to incorrectly at previous encounter). **(C)** Neuroimaging will address interactions of the pMFC with Hip and visual areas (Vis) representing stimulus orientation (V1) and faces ("fusiform face area"). **(D)** Hypothetical effects of ACh and synaptic integrity of the innervated cortex on cognitive performance (from Dumas and Newhouse, 2011).

Collaborations: **TP12** Düzel (recruitment of participants after amyloid PET) **TP10** Stork (cholinergic modulation of network activities), **TP8** Seidenbecher/Gundelfinger (synapse modification mechanisms of cholinergic modifiers).

References:

Danielmeier, C., Allen, E. A., Jocham, G., Onur, O. A., Eichele, T., **Ullsperger, M.** (2015) Acetylcholine mediates behavioral and neural post-error control. Curr Biol, **25**, 1461-1468.

Dumas, J. A., Newhouse, P. A. (2011) The cholinergic hypothesis of cognitive aging revisited again: cholinergic functional compensation. Pharmacology, biochemistry, and behavior, **99,** 254-261.

Hammer, A., Tempelmann, C., Munte, T. F. (2013) Recognition of face-name associations after errorless and errorful learning: an fMRI study. BMC Neurosci **14**, 30.

Hester, R., Barre, N., Murphy, K., Silk, T. J., Mattingley, J. B. (2008) Human medial frontal cortex activity predicts learning from errors. Cereb Cortex, **18**, 1933-1940.

Janeczek, M., Gefen, T., Samimi, M., Kim, G., Weintraub, S., Bigio, E., Rogalski, E., Mesulam, M. M., Geula, C. (2017) Variations in Acetylcholinesterase Activity within Human Cortical Pyramidal Neurons Across Age and Cognitive Trajectories. Cereb Cortex, 1-9.

Klein, T. A., Neumann, J., Reuter, M., Hennig, J., von Cramon, D. Y., **Ullsperger, M.** (2007) Genetically determined differences in learning from errors. Science, **318**, 1642-1645.

Potts, R., Shanks, D. R. (2014) The benefit of generating errors during learning. J Exp Psychol Gen, **143**, 644-667.

Rodriguez-Fornells, A., Kofidis, C., Munte, T. F. (2004) An electrophysiological study of errorless learning. Brain Res Cogn Brain Res, **19**, 160-173.

Ullsperger, M., Danielmeier, C., Jocham, G. (2014) Neurophysiology of performance monitoring and adaptive behavior. Physiol Rev, **94**, 35-79.

Wessel, J. R., Danielmeier, C., Morton, J. B., **Ullsperger, M.** (2012) Surprise and error: common neuronal architecture for the processing of errors and novelty. J Neurosci, **32**, 7528-7537.