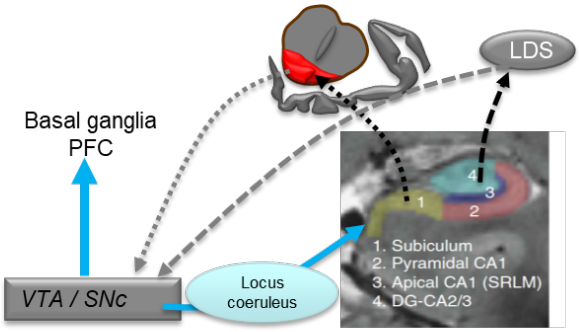
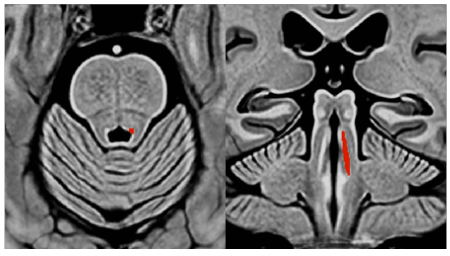
TP12: Effects of L-DOPA on memory consolidation in high- and low-performing amyloid-negative older adults (Emrah Düzel)

When compared to young adults, healthy older adults have poorer episodic memory (Duzel, Schutze et al. 2011). The cause of this age-related decline is still not fully understood. A major challenge in the investigation of memory impairment associated with healthy aging is the potential presence of incipient, preclinical dementia pathology (Villemagne, Burnham et al. 2013). Such a pathology must be excluded, for instance through molecular imaging with PET, in order to stratify older adults as healthy agers. However, to date, very little is known about the variability of episodic memory capabilities in populations in which dementia pathology has been excluded.

In Alzheimer's Disease amyloid PET allows detection of amyloid pathology 10 to 20 years before the onset of clinical dementia symptoms and in over 65 year old adults, the preclinical presence of amyloid pathology can be found in 30 % of individuals (Villemagne, Burnham et al. 2013). When this preclinical AD has been excluded, a major source of variability of memory performance and of poorer memory compared to young adults could be age-related dysfunction of dopaminergic and noradrenergic neuromodulation which can putatively occur independently of amyloid-pathology (Backman, Nyberg et al. 2006). Given the role of dopamine and noradrenaline in memory encoding and consolidation, loss of dopaminergic and noradrenergic drive can be hypothesized to impair long-term episodic memory in old age (Lisman, Grace et al. 2011, Chowdhury, Guitart-Masip et al. 2012). Both systems are mutually dependent because noradrenergic neurons receive dopaminergic drive and, in turn, may release dopamine the hippocampus (Smith and Greene 2012).



Hippocampal subfields can modulate SN/VTA activity through a ventral striatal and a latero-dorsal septal (LDS) pathway. The ensuing dopamine release in the medial temporal lobe is believed to require the locus coeruleus and SN/VTA projections. The integrity of the locus coeruleus can be measured with neuromelanin sensitive MRI (bottom half of the figure; see Betts et al, 2017).



Hypothesis: We postulate that low performing, amyloid-free older healthy individuals will have lower integrity of dopaminergic and noradrenergic midbrain regions compared to those who are high performing. Thus, treatment with a single dose of L-DOPA will improve memory consolidation for events encoded under L-DOPA in low performing older adults. Furthermore, the degree of improvement will depend on the integrity of the locus coeruleus (LC), origin of noradrenalin in the human brain. We define the following Aims:

1. To determine to what extent the integrity of dopaminergic and noradrenergic midbrain regions explains variance of episodic memory consolidation in amyloid-free healthy older adults.
2. We will investigate whether memory consolidation can be improved in low and high performing healthy older adults by substituting dopamine.

Collaborations: TP4 Kreutz (impact of insulin resistance on memory dysfunction), **TP13** Ullsperger (joint recruitment of participants after amyloid PET), **TP10** Stork and **TP11** Leßmann (excitability and network modulation in the rodent hippocampus).

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