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Contribution of norepinephrine to emotional memory consolidation during sleep

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Summary
Background: There is increasing evidence indicating that slow wave sleep (SWS) supports memory consolidation. This effect may in part originate from phasic noradrinergic (NE) activity occurring during SWS in the presence of tonically lowered NE levels. Here, we examined whether NE supports the consolidation of amygdala-dependent emotional memory during SWS.
Methods: In a double-blind cross-over study, 15 men learned emotional and neutral materials (stories, pictures) in the evening before a 3-h period of early SWS-rich retention sleep, during which either placebo or clonidine, an α2-adrenoceptor agonist which blocks locus coeruleus NE release, was intravenously infused. Memory retrieval as well as affective ratings and heart rate responses to the pictures were assessed 23 h after learning.
Results: Clonidine reduced plasma NE levels but had no effect on SWS. While retention of story content words and pictures per se remained unaffected, clonidine distinctly blocked the superiority of emotional compared to neutral memory for temporal order, with this superiority of emotional over neutral memories observed only in the placebo condition. Heart rate responses to pictures were not affected, but whereas under placebo conditions familiar negative pictures were rated less arousing and with a more negative valence compared to pictures not seen before; these differences were abolished after clonidine.
Conclusion: Given that memory for the temporal order of events depends on the hippocampus to a greater extent than item memory, our findings suggest that NE activity during early SWS-rich sleep facilitates consolidation of memories that involve both, a strong amygdalar and hippocampal component.

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1. Introduction

Sleep is known to support memory consolidation (Maquet, 2001; Stickgold, 2005). However, the underlying mechanisms are unclear. Declarative memory predominantly benefits from early sleep with high amounts of slow wave sleep (SWS; Peigneux et al., 2001; Diekelmann et al., 2009). During SWS, reactivation of previously learned materials is assumed to strengthen memories by promoting the redistribution of the new representations from hippocampal preferentially to neocortical circuitry for long-term storage (McClelland et al., 1995; Buzsaki, 1998; Diekelmann and Born, 2010). Such processes of sleep-dependent consolidation have been shown to critically depend on characteristic changes in neurotransmitter and hormone release during sleep, e.g., acetylcholine and cortisol (Born et al., 1999; Born and Wagner, 2004; Gais and Born, 2004).

Norepinephrine (NE) likewise displays a pronounced sleep-dependent regulation and is well-known to be functionally implicated in memory consolidation, especially of emotional memory (van Stegeren, 2008; McGaugh and Roozendaal, 2008). Compared to wakefulness, NE levels distinctly decrease during SWS and reach minimum concentrations during rapid eye movement (REM) sleep (Aston-Jones and Cohen, 2005; Rasch et al., 2007). The locus coeruleus (LC), which is the main source of cortical NE, projects to multiple brain areas including amygdala, hippocampus and neocortical areas (Young, 1993; Petrovich et al., 2001). Although LC activity rapidly declines after sleep onset, transient firing bursts were detected in LC neurons in rats during SWS (Aston-Jones and Bloom, 1981), which appeared to occur in response to preceding learning-related episodes, possibly in conjunction with reactivation of the learned materials (Eschenko and Sara, 2008). In humans, suppression of NE release by the α2-adrenoceptor agonist clonidine during SWS-rich retention sleep impaired consolidation of odor memories, whereas the noradrenergic reuptake inhibitor reboxetin improved consolidation (Gais et al., 2011). Like for emotional memories, storage of odors critically involves the amygdala, together with hippocampal function (Gall et al., 1998; Li et al., 2006). Concurrent activation of amygdala and hippocampus via direct and indirect NE pathways appears to be critical for the formation of emotional, episodic and odor memories (Petrovich et al., 2001; Strange and Dolan, 2004). Yet, the role of NE for consolidating emotional memory during sleep has not been investigated so far.

Here, we tested whether suppression of NE impairs memory consolidation during early SWS-rich sleep, particularly of emotional memories. For this purpose, we measured effects of clonidine, infused to generally suppress noradrenergic output from LC, on retention of the contents of and on the temporal order in neutral and emotional stories across 3-h periods of early SWS-rich sleep. Additionally, we assessed retention of emotional and neutral pictures and corresponding subjective ratings as well as heart rate responses.

2. Methods

2.1. Participants

Fifteen native German speaking healthy men (mean $\pm$ SD age: 22.87 $\pm$ 3.42 yrs, range 19–28 yrs, body mass index: 20–25) were recruited at the University of Luebeck. All were non-smokers, free of medication and had no history of neurological, psychiatric or endocrine disorders, and were instructed to follow a normal sleep–wake rhythm for at least four weeks before the experiments, which was ensured by a questionnaire. Prior to the experiments, subjects were accustomed to sleeping under laboratory conditions during an adaptation night, including placement of intravenous catheters. On experimental days they were required to get up at 0700 h and not to consume caffeine or alcohol. The study was approved by the ethics committee of the University of Luebeck and all participants gave written informed consent prior to participation.

2.2. Substance administration

Clonidine (112.5 μg Clonidin ratiopharm®, Ratiopharm GmbH, Ulm, Germany) was dissolved in 17 ml saline solution and infused within 10 min at a rate of 100 ml/h. Clonidine is an adrenoceptor agonist that binds with ten times higher affinity to α2- than α1-receptors resulting in a predominant reduction of sympathetic activity, increase of the vagal tone and blockade of the release of norepinephrine. Intravenous administration of clonidine is centrally effective within a few minutes reaching its maximum within 20–30 min. Elimination half-life is 8–15 h. Clonidine has been shown to markedly reduce REM sleep while having no effect on the amount of SWS (Spiegel and Devos, 1980; Gais et al., 2011).

2.3. Design and procedure

The study was conducted according to a double-blind, within-subject cross-over design with the order of conditions (placebo vs. clonidine) balanced across subjects and an interval of at least two weeks between the subject's two conditions (Fig. 1A). Each condition started with a learning phase ($\sim$2100–2230 h), followed by a 3-h period of retention sleep during which substances were infused. Memory retrieval was tested the next evening ($\sim$2030–2130 h) to allow the retest session to start as soon as possible after awakening to keep the influence of partial sleep deprivation low, but simultaneously ensure that most of the substance was washed out.

In each condition, participants reported to the laboratory at 1830 h for preparing standard polysomnographical and electrocardiographic (ECG) recordings and for the placement of indwelling venous catheters (one in each forearm) that were connected to long thin tubes to enable substance infusion and blood collection from an adjacent room without the subject's awareness. Additionally, before going to bed a cuff was attached to the upper arm for measuring blood pressure. Before the learning phase (see below), vigilance performance was assessed on a 5-min version of the Psychomotor Vigilance Test (PVT; Roach et al., 2006) and the day's mood was assessed by the Positive and Negative Affect Scale (Watson et al., 1988).

Lights were turned off at 2300 h. As soon as polysomnographical recordings showed signs of sleep stage 2 for more than 1 min, placebo (saline solution) or clonidine administration was initiated. Participants were awakened 3 h after sleep onset and stayed awake till retrieval testing in the next evening. Until 0600 h, they were under supervision of the