



Sex and modulatory menstrual cycle effects on sleep related memory consolidation

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Summary The benefit of sleep in general for memory consolidation is well known. The relevance of sleep characteristics and the influence of hormones are not well studied. We explored the effects of a nap on memory consolidation of motor (finger-tapping-task) and verbal (associated-word-pairs) tasks in following settings: A: young, healthy males and females during early-follicular phase ($n = 40$) and B: females during mid-luteal and early-follicular phase in the menstrual cycle ($n = 15$).

We found a sex and in women a menstrual cycle effect on memory performance following a nap. Men performed significantly better after a nap and women did so only in the mid-luteal phase of their menstrual cycle. Only the men and the women in their mid-luteal phase experienced a significant increase in spindle activity after learning. Furthermore, in women estrogen correlated significantly with the offline change in declarative learning and progesterone with motor learning. The ratio of the 2nd and 4th digit, which has been associated to fetal sex hormones and cognitive sex differences, significantly predicted the average performance of the female subjects in the learning tasks.

Our results demonstrate that sleep-related memory consolidation has a higher complexity and more influencing factors than previously assumed. There is a sex and menstrual cycle effect, which seems to be mediated by female hormones and sleep spindles. Further, contrary to previous reports, consolidation of a simple motor task can be induced by a 45 min NREM sleep nap, thus not dependent on REM sleep.

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1. Introduction

Memory benefits from sleep whether it is a whole night (Diekelmann and Born, 2010) or just a short nap (Mednick et al., 2003, 2008; Tucker et al., 2006; Korman et al., 2007).

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Up until now slow wave sleep (Fowler et al., 1973), sleep spindles (Gais et al., 2002; Schabus et al., 2004; Clemens et al., 2005; Schmidt et al., 2006; Genzel et al., 2009), and REM sleep (Smith et al., 2004) have been indicated to play individual roles in this offline consolidation of different memory types, or may even interact in a sequential function (Ambrosini and Giuditta, 2001). However, most studies neglect to control for sex or, in women, for menstrual cycle (Cahill, 2006), even though sex and menstrual effects have been reported both on sleep (Ishizuka et al., 1994; Driver et al., 1996; Manber and Armitage, 1999) and online-learning, with online-learning implying periods during which subjects actively engage in learning in contrast to offline-learning without any conscious learning activity (Hampson, 1990; Lewin et al., 2001; Maki et al., 2002). Women in general have twice as many sleep spindles and more slow wave sleep than men (Manber and Armitage, 1999; Steiger, 2003; Dzaja et al., 2005). Interestingly, women experience a significant decrease in EEG activity in the frequency range of sleep spindles during their menses (Driver et al., 1996) and spindle frequency itself is highest before, on the decline during, and lowest after the menses (Ishizuka et al., 1994). This may impact on sleep-related memory consolidation, in which sleep spindles seem to play a crucial role (Gais et al., 2002; Schabus et al., 2004; Clemens et al., 2005; Schmidt et al., 2006; Genzel et al., 2009). With regard to online learning, women tend to perform at a higher level than men on most verbal and fine motor tasks while men outperform women on visual-spatial tasks (Lewin et al., 2001; Cahill, 2006; Andreano and Cahill, 2009). Of note, on tasks in which women typically score better than men, women score higher during mid-luteal phase (high estrogen and progesterone) than within menstrual phase (low estrogen and progesterone) (Hampson, 1990; Maki et al., 2002). On tasks in which men typically outperform women, women do best during menses (Hampson, 1990; Maki et al., 2002). These menstrual effects are most likely mediated by the female hormones estrogen and progesterone (Maki et al., 2002).

However, sex differences are most likely not only based on transient activation effects of hormones, but even more on structural and organizational differences that impact performance differences. For example the 2D:4D digit ratio has been shown to predict the "maleness" or "femaleness" of the brain with males having lower ratios and females higher (Poulin et al., 2004). Female index (2D) and ring (4D) finger are of approx. the same length, while men in average have a larger 4D than 2D leading to a smaller 2D:4D digit ratio. Interestingly, women with a lower 2D:4D ratio are better at "male" learning e.g. spatial as well as numerical ability (Csatho et al., 2003; Kempel et al., 2005), while women with higher 2D:4D ratios are better at "female" learning e.g. picture free recall (Poulin et al., 2004). This is most likely a result of digit and urinogenital system formation both being dependent on the homeobox genes Hox a and d. A significant negative association between 2D:4D ratio and the fetal testosterone relative to fetal estrogen was found in humans and mice (Lutchmaya et al., 2004; Zheng and Cohn, 2011).

Targeting the effects of sex on sleep-related memory consolidation, in an initial study we tested healthy, young men and women in their menses. We additionally tested healthy females according to similar protocols in a within-study design to investigate menstrual cycle effects on sleep

related memory consolidation during a nap. The purpose of the study is to uncover sex and menstrual cycle effects on sleep related memory consolidation, which have been neglected so far.

2. Experiment 1

2.1. Methods

2.1.1. Subjects

The experimental subjects were healthy volunteers ($n = 40$; 20 males and 20 females) aged 18–30 years. They were recruited mainly via the medical school and were paid for the participation in the study. The subjects were first screened for psychiatric, physical, or sleep disorders with semi-structured interviews, physical examination and the Pittsburgh Sleep Quality Index (Buysse et al., 1989). Additionally, we obtained urinary-drug-screening and routine blood tests (blood cell count, electrolytes, liver and kidney function, thyroid hormones). Further exclusion criteria were: shift-work at night, a transmeridian flight or any medical treatment during the last three months, substance abuse, professional piano playing (more than 5 years intensive training), professional type writing, extreme chronotypes and regular naps. The female subjects had a regular menstrual cycle of 28–32 days and did not take any hormonal contraceptives. The regularity of the menstrual cycle was assessed by inquiring about the average length and the variability of the menstrual cycle over the last six months during the general entrance interview. The subjects were randomly assigned to two different groups: NAP and WAKE. Each group (NAP and WAKE) consisted of 10 females and 10 males. The subjects of all four groups had a similar educational background (university students) and similar age-range (Nap-male 23.3 ± 2.6 , Nap-female 23.0 ± 3.5 , Wake-male 23.1 ± 2.2 , Wake-female 22.9 ± 2.6). For the female subjects the first and second study block started in the follicular phase during the first week of their menstrual cycle when estrogens are low.

The participants of both experiments agreed to have regular sleep patterns throughout the experiment and kept a sleep diary for the week preceding the study blocks. The Ethics Committee of the Ludwig Maximilian University Faculty of Medicine, Munich, Germany, approved the research project. The experiments were undertaken with the understanding and written consent of each subject, and the study conforms to The Code of Ethics of the World Medical Association.

2.1.2. Procedures

The subjects were randomly divided into two groups: NAP and WAKE. The NAP group underwent two experimental study blocks while the WAKE group participated only in the first study block. The first study block was composed of an afternoon in the sleep laboratory with learning tasks and a nap (learning nap: L-NAP) or a movie (WAKE). The second study block of the NAP group consisted of only a nap without learning tasks (control nap: C-Nap), to analyze the effect of learning on sleep parameters (see Fig. 1).

For the first study block the subjects arrived at 13:00 h; they first completed the D2 Concentration test

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