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Research Report

# Too much of a good thing? Elevated baseline sleep spindles predict poor avoidance performance in rats

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ABSTRACT

Sleep spindles may be involved in synaptic plasticity. Learning-dependent increases in spindles have been observed in both humans and rats. In humans, the innate (i.e., baseline) number of spindles correlate with measures of academic potential such as Intelligence Quotient (IQ) tests. The present study investigated if spindles predict whether rats are able to learn to make avoidance responses in the two-way shuttle task. Baseline recordings were taken continuously for 24 h prior to training on the two-way shuttle task for 50 trials/day for two days followed by a 25 trial re-test on the third day. At re-test, rats were categorized into learners ($n=16$) or non-learners ($n=21$). Groups did not differ in baseline duration of rapid eye movement sleep, slow wave sleep, wake or spindle density. For combined groups, spindle density in the 21 to 24-hour period but not at any other period during baseline was negatively correlated with shuttle task performance at re-test. Conversely, the learning-related change in spindle density in the 21 to 24-hour period, but not at any other time after the first training session was positively correlated with shuttle task performance. Rats in the non-learning condition have a higher number of spindles at baseline, which is unaffected by training. On the other hand, learning rats have fewer spindles at baseline, but have a learning-related increase in spindles. Extreme spindle activity and high spindle density have been observed in humans with learning disabilities. Results suggest that while spindles may be involved in memory consolidation, in some cases, high levels of spindles prior to training may be maladaptive.



## 1. Introduction

The functions of sleep remain largely enigmatic, but one of the dominant hypotheses is that sleep plays an important role in the formation of new memories. Sleep spindles may provide an electrophysiological signature of a potential mechanism for sleep-dependent memory consolidation. Sleep spindles are one of the defining characteristics of non-rapid eye movement (non-REM) sleep. Spindles predominate in Stage 2 sleep, but also occur during slow wave sleep (Stages 3 and 4; SWS). Spindles have a fusiform shape that is high (voltage) in the middle and tapers at either end, oscillate from 11 to 16 Hz and last about 0.25 to 3 s.

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In humans, the density of sleep spindles appears to be consistent for any individual from night-to-night (De Gennaro et al., 2005; Gaillard and Blois, 1981; Silverstein and Levy, 1975); it has been remarked that inter-individual characteristics in sleep spindle density are reliable enough to serve as an "electrophysiological fingerprint" (De Gennaro et al., 2005). The functional significance of sleep spindles has not been investigated until recently. Inter-individual differences in sleep spindle density may be a physiological marker for intellectual ability as measured by aptitude tests that typically use the age-normed Intelligence Quotient (IQ). Sleep spindle density has been found to be positively correlated with performance on the Multidimensional Aptitude Battery-II (Fogel et al., 2007a,b), Raven's progressive matrices test (Bódizs et al., 2005), Wechsler Memory Scale (Schabus et al., 2006) and visuospatial memory ability (Bódizs et al., 2008). Sleep spindle density has been found to be positively correlated with overnight verbal memory retention (Gais et al., 2002; Clemens et al., 2005) and overnight visuospatial memory retention (Clemens et al., 2006). Schabus et al. (2004) found that individuals with increased spindle activity during Stage 2 sleep had increased recall from pre-sleep to post-sleep testing, whereas those who did not have increased spindle activity did not improve on the task. Learning-dependent increases in sleep spindle density have been observed following motor procedural learning (Fogel and Smith, 2006; Fogel et al., 2007a, b) and are thought to be a putative marker of consolidation.

In rats, it has been demonstrated that induction of long-term potentiation (LTP) results in increased reliability of evoked sleep spindles (Werk et al., 2005) and conversely, that sleep spindle-like activity can produce LTP in preparations of rat somatosensory cortex *in vitro* (Rosanova and Ulrich, 2005). *In vivo* studies have demonstrated that sleep spindle density increased following reward learning in rats; when the reward was available noncontingently, there was no subsequent change in sleep spindles (Eschenko et al., 2006).

Critical and discrete (about 4-hour) post-learning periods marked by increased REM sleep (termed REM sleep windows) have been identified in the rat (for review see Smith, 1985, 1996, 2003). Recently, we have identified learning-related increases in sleep spindle density (from 21–24 h post training) following avoidance learning in rats that occurred immediately following the REM sleep window (from 17–20 h post training; Fogel et al., 2009). These results suggest that sleep-dependent memory consolidation may occur in (at least) two sequential steps and provide support for the sequential hypothesis, initially proposed by Giuditta (first described by Giuditta (1977, 1985); see Giuditta et al. (2003) for a recent review of the sequential hypothesis).

Sleep spindles may be involved in hippocampal–neocortical dialogue taking place during SWS (Siapas and Wilson, 1998), and may be an important mechanism or identifiable feature in the electroencephalogram (EEG) related to sleep-dependent memory consolidation. The present study investigated the relationship between baseline sleep architecture and sleep spindles with shuttle avoidance performance to identify sleep EEG predictors of the ability to learn. Based on our previous results (Fogel et al., 2009) it was predicted that sleep spindles during the 21 to 24-hour baseline period (aligned to lights on) may predict avoidance performance.

## 2. Results

### 2.1. Behavioural data

Rats were clearly distinguished as either learning or non-learning rats at re-test according to previously reported criteria (Fogel et al., 2009). Learning rats increased avoidance responses over the training and testing sessions, whereas the non-learning rats did not (Fig. 1). A 2×3 (group×day) ANOVA for avoidance responses revealed a significant group by day interaction ($F(2,70)=13.82$, $p<0.0001$). Avoidance responses significantly increased over the training and testing days as revealed by follow-up simple effects repeated measures ANOVAs for the learning group ($F(2,30)=23.43$, $p<0.0001$). Post-hoc *t*-tests revealed that there was a significant increase in avoidance responses for learning rats from Training Day 1 to Training Day 2 ($t(15)=5.50$, $p=0.00006$), and no change from Training Day 1 to re-test ($t(15)=1.63$, $p>0.05$) indicating that performance had reached asymptote by re-test. No significant change was observed in the non-learning condition ($F(2,40)=0.32$, $p=0.73$).

### 2.2. Sleep architecture data

There were no significant group differences between the learning and non-learning groups at baseline for REM sleep ($F(5,165)=1.31$, $p=0.26$), SWS ($F(5,165)=0.76$, $p=0.58$) or wake ($F(5,165)=1.19$, $p=0.32$) across the six 4-hour periods (Table 1). The groups did not differ significantly in the number of sleep spindles/min across the six 4-hour baseline recording periods ($F(5,145)=1.10$, $p=0.36$; Table 2).

### 2.3. Predictors of shuttle avoidance performance

The percent total duration of REM, SWS and wake did not predict shuttle avoidance performance in any of the baseline recording periods (Table 1). Baseline spindle density for all rats significantly negatively correlated with shuttle avoidance performance at re-test only in the 21 to 24-hour period

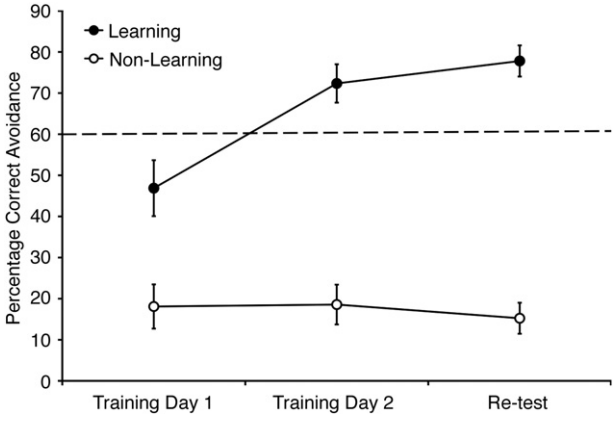


**Fig. 1 – Mean percent correct avoidances at Training Days 1, 2 and re-test. Rats performing above 60% criterion (dashed horizontal line) at re-test are indicated by filled circles ($n=16$), and unfilled circles for non-learning rats ($n=21$). Error bars represent standard error of the mean.**