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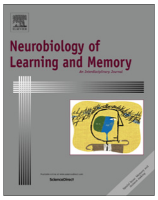

Impaired extinction of fear conditioning after REM deprivation is magnified by rearing in an enriched environment

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ABSTRACT

Evidence from both human and animal studies indicates that rapid eye movement sleep (REM) is essential for the acquisition and retention of information, particularly of an emotional nature. Learning and memory can also be impacted by manipulation of housing condition such as exposure to an enriched environment (EE). This study investigated the effects of REM deprivation and EE, both separately and combined, on the extinction of conditioned fear in rats. Consistent with prior studies, conditioning was enhanced in EE-reared rats and extinction was impaired in REM deprived rats. In addition, rats exposed to both REM deprivation and EE showed the greatest impairment in extinction, with effects persisting through the first two days of extinction training. This study is the first to explore the combination of REM deprivation and EE and suggests that manipulations that alter sleep, particularly REM, can have persisting deleterious effects on emotional memory processing.

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1. Introduction

Sleep has long been thought to play an integral role in a variety of tasks, including learning and memory. Although both rapid eye movement sleep (REM) and non-REM sleep (NREM) play a role in the acquisition and retention of information, recent findings have suggested that the stabilization of information in long-term memory is dependent on REM (Rasch & Born, 2013) and that REM is particularly important for memories with emotional content (Walker, 2010).

The importance of REM for both acquisition and retention has been demonstrated in numerous and varied tasks. For example, REM deprivation (RD) impairs spatial learning in the Morris water maze (Smith & Rose, 1996). RD also impairs the extinction of fear conditioning. Specifically, rats exposed to RD for 6 h after fear conditioning demonstrated impaired acquisition of extinction learning (Hunter, 2014; Silvestri, 2005; Silvestri & Root, 2008). In a similar study, rats exposed to RD following a session of extinction training demonstrated impaired retention of extinction learning (Fu et al., 2007). Consistent with these findings are studies demonstrating alterations in REM time following fear conditioning and extinction. For example, REM is suppressed following fear conditioning (Sanford, Silvestri, Ross, & Morrison, 2001) and increased after extinction training (Wellman, Yang, Tang, & Sanford, 2008). Sleep recording after extinction training has revealed that the amount of time spent in REM varies predictably by retention of extinction learning. Specifically, animals that successfully acquired extinction during training and also retained it in a test conducted 24 h later showed a prolonged (4 h) increase in REM after extinction training. In contrast, animals that successfully acquired extinction but failed to retain it showed only a transient (2 h) increase in REM (Datta & O'Malley, 2013). The neurobiological link between REM and extinction may be the hippocampus, as low frequency hippocampal stimulation eliminated the increase in REM due to extinction training and also impaired the retention of prior extinction learning (Deschaux et al., 2010).

Learning and memory can also be affected by manipulations of housing condition. For example, a large body of research has demonstrated beneficial effects of rearing rats in an enriched environment (EE). In this design, rats are housed in large cages with increased opportunity for exploratory behavior and social interaction. Typical enriched environments include a variety of frequently replaced toys, nesting materials, and running wheels as well as an increased number of rats housed together to enhance social interaction. EE exposure has both neurobiological and behavioral effects. A variety of alterations have been observed in the hippocampus, including increased neurogenesis (Kempermann, Kuhn, & Gage, 1997), enhanced long-term potentiation (Duffy, Craddock, Abel, & Nguyen, 2001; Green & Greenough, 1986), increased synaptic density (Rampon et al., 2000), and enhanced arborization of dendrites (Leggio et al., 2005). More recent work has indicated that EE can alter neurobiological variables in a number of brain areas including structures known for their role in fear

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conditioning and extinction such as the amygdala (Okuda et al., 2009) and prefrontal cortex (Sampedro-Piquero, Zancada-Menendez, Begega, Rubio, & Arias, 2013).

Consistent with these neurobiological effects, EE exposure results in improved performance in hippocampal-dependent tasks. Rats reared in an EE demonstrate enhanced performance in the Morris water maze (Kempermann et al., 1997; Nilsson, Perfilieva, Johansson, Orwar, & Eriksson, 1999), radial arm maze (Leggio et al., 2005), radial arm water maze (Sampedro-Piquero et al., 2013), contextual fear conditioning (Rampon et al., 2000) and novel object recognition memory task (Birch, McGarry, & Kelly, 2013). However, the effects of EE exposure are not limited to hippocampal-dependent tasks. Alterations in the acquisition and extinction of cued fear conditioning, which is more reliant on the amygdala than the hippocampus (Phillips & LeDoux, 1992), as a consequence of EE exposure have also been investigated. Most studies have shown increased conditioned freezing in EE-reared animals when measured during a single conditioned stimulus (CS) alone retention trial (Duffy et al., 2001; Rampon et al., 2000; Tang, Wang, Feng, Kyin, & Tsien, 2001; Zanardi et al., 2007; but see Mitra & Sapolsky, 2008). However, there is substantially less research investigating the extinction of conditioned fear. In one study, EE-reared rats showed greater freezing than rats reared in standard housing conditions during the first trial of extinction training, which may be reflective of a stronger memory for conditioned fear learning. However, with additional extinction trials, EE-reared rats showed enhanced extinction (Tang et al., 2001). Another study found impaired extinction in EE-reared mice on the second and third days of extinction training of a cued conditioning task but no effect of housing condition on the first day (Pietropaolo, Feldon, Alleva, Cirulli, & Yee, 2006). In contrast, at least one study observed no effect of EE on the acquisition, extinction, or renewal of cued or contextual fear conditioning (Mitra & Sapolsky, 2008). Taken together, these findings indicate that EE likely produces an enhanced learning of the CS–US association but the effects of EE exposure on extinction remain unclear.

EE exposure has also been shown to alter sleep architecture. Specifically, REM is increased by EE exposure (Gutwein & Fishbein, 1980; Mirmiran, van den Dungen, & Uylings, 1982) as well as exposure to some of the commonly used components of an EE such as group housing and novel object interaction (Febinger, George, Priestly, Toth, & Opp, 2014). More specifically, EE-reared rats showed greater overall sleep time and a shorter REM latency (Mirmiran et al., 1982). Based on these effects, it is possible that rearing animals in an EE may provide some degree of protection against the impairing effects of RD on the extinction of conditioned fear.

The present study was designed to characterize the effects of RD in combination with EE exposure on the extinction of conditioned fear to both a cue and context. In addition, extended extinction training was conducted to assess the long-term effects of RD and EE on extinction. Given the previously observed effects of EE exposure on sleep parameters including increased REM (Mirmiran et al., 1982), possible interactions between the EE and RD conditions were of particular interest.

2. Materials and methods

2.1. Subjects

The subjects were 28 male Sprague–Dawley rats (Harlan, Indianapolis) obtained at 6 weeks of age. Upon arrival in the vivarium, rats were randomly assigned to the standard housing (SH; $n = 14$) or EE ($n = 14$) condition. Food and water were available *ad libitum*. All procedures were approved by the Seton Hall University Institutional Animal Care and Use Committee and followed the guidelines for the care and use of animals from the United States Public Health Service.

2.2. Housing

The SH condition consisted of 47 × 26 × 21 cm Plexiglas cages with wire tops (Ancare, Bellmore, NY) and corncob bedding with rats housed two or three per cage. The EE consisted of a 76.2 cm × 45.7 cm × 91.4 cm cage with wire mesh sides and a solid plastic floor (model R-695, Martin's Cages, Columbia, PA) with corncob bedding. The cage had three levels with ramps for access between levels. Assorted objects (e.g., cardboard tubes, chew sticks, wooden hut) were placed in the cage with old objects removed and new objects added once each week. Four rats were housed in each EE cage. Rats were maintained in their respective housing condition for six weeks prior to commencement of fear conditioning and RD procedures and remained there for the duration of the study.

2.3. Fear conditioning and extinction

Fear conditioning and extinction procedures were identical to those described previously (Silvestri & Root, 2008), with the addition of a third extinction session. Briefly, animals were placed in the conditioning chambers and presented with 10 CS + US pairings (CS: 30 s white noise coterminating with a 0.5 s, 1.0 mA footshock US, variable 120 s intertrial interval). Immediately after completion of conditioning, animals were placed in the RD or control apparatus (nonRD condition) for 6 h (see Section 2.4 for details). This resulted in a total of four experimental groups: SH + RD ($n = 8$), SH + nonRD ($n = 6$), EE + RD ($n = 7$), and EE + nonRD ($n = 7$). Forty-eight hours after the initial conditioning session, an extinction session was conducted in which animals were placed in the conditioning chambers and presented with 10 CS alone trials. A second and third extinction session identical to the first were conducted at 48 h intervals after the first session. Due to equipment malfunction, data from the third extinction session were lost for two EE rats, one each from the RD and nonRD group. Freezing, which is a reliable indicator of the level of conditioning, was defined as the absence of all movement except as necessary for respiration (Bolles & Collier, 1978). Freezing was measured with a time-sampling procedure by a trained observer blinded to experimental condition. Level of fear to the context was assessed by measuring freezing before each CS presentation, while fear to the cue was determined by freezing during the CS itself.

2.4. REM deprivation

RD procedures were identical to those described previously (Silvestri & Root, 2008). Briefly, rats in the RD condition were placed on an inverted flowerpot inside a large pail filled with water up to 7 cm below the level of the flowerpot (Mendelson, Guthrie, Frederick, & Wyatt, 1974). Rats in this condition can obtain NREM but lose their balance on the flowerpot at the onset of REM, thereby terminating the REM episode. This technique does not significantly affect time in NREM (Mendelson et al., 1974; Smith & Gisquet-Verrier, 1996) but likely produces a fragmentation of sleep due to repeated awakenings. Rats in the nonRD condition were placed in a similar apparatus with a larger platform which permitted the occurrence of REM (Chase & Morales, 1990; Mendelson et al., 1974). At the end of the six hour period rats were returned to their home cages and left undisturbed until extinction training (approximately 39 h later).

2.5. Statistical analysis

Mixed design ANOVAs were computed with IBM SPSS version 20 statistical software. Conditioning data were analyzed with

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