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The Role of Sleep in Fear Learning and Memory

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Abstract

During the last 10 years, a large body of studies have used fear conditioning paradigms to study the role of sleep in the consolidation of fear and safety learning. This line of research could allow us to answer if it is adaptive or not to sleep in the aftermath of a negative experience, and if sleep has a role in consolidating extinction learning. This field has so far produced several contrasting findings. Thus, this review will not deliver many clear conclusions, but will instead be an attempt to summarize what we know at the moment, to describe the potential clinical applications of this research, and to discuss where to go from here.

1. Introduction

Should sleep be promoted or actively avoided in the immediate aftermath of a negative experience? Does sleep have a role in consolidating the memory of learning that something previously associated with danger should now be considered safe? These are the questions that could be answered by using fear conditioning paradigms to study the link between sleep and memory. This paradigm has in a large body of work been used as a laboratory model of a negative experience. An overview of it is presented in Figure 1. This review will focus only on studies in humans, and the main focus will be on papers published within the last five years. However, considering that this is still an emerging, albeit rapidly growing, field, it has been possible to mention all the studies that have so far been published on this topic within the scope of this review paper.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

2.1. Sleep and fear recall

It has been established that sleep has a role in consolidating memory [1] and in processing information such that we can draw conclusions and make generalizations [2]. The question thus, has been raised whether it is adaptive to sleep right after a negative experience, or if doing so might risk increasing the negative reaction when one later encounters a reminder of it (by memory consolidation). Moreover, sleep might also risk having the aversive reaction "spill over" also to other stimuli that should not merit a fear response (by generalization). Studies have so far yielded highly contrasting results. Menz et al. found larger ***fear recall*** when conditioning was followed by sleep, as compared to sleep deprivation, with sleep, and especially Rapid Eye Movement (REM) sleep, decreasing responses to the CS- (see text box). Another study found, in comparison with wakefulness, increased fear recall after late sleep (which is rich in REM sleep), but no such effects after early sleep (which has very little REM sleep) [4]. Increases in REM sleep during the post-conditioning night as compared with a baseline night have also been found to be correlated with fear recall [5]. Contrary to these studies, other work has found entirely opposite results, with greater fear recall following time spent awake than following a daytime nap [6*]. This study also included ***generalization*** stimuli during the re-test. Results revealed a tendency for a more generalized response after sleep; responses were similar to all stimuli regardless of similarity to the CS+ (see text box). Similarly, unpublished data from Lerner et al. found that sleep, and especially REM sleep, reduced fear recall but increased fear responses to generalization stimuli with high fear relevance. Two other studies have reported no effects of sleep on either fear recall or generalization [7, 8]. Thus, the jury is still out when it comes to the effect of sleep on the consolidation and generalization of fear conditioning.

It is also important to mention that greater fear recall is not necessarily a bad thing, considering that is important to be able to differentiate between safe and dangerous stimuli. Lower differential fear recall does not necessarily mean less fear, just a lack of discrimination between stimuli, possibly with high responses to both. A potential application for this line of research, and a strong argument for why more studies are needed, is to determine if avoidance or promotion of sleep right after a traumatic experience changes the risk of developing post-traumatic stress disorder (PTSD). This condition is strongly characterized by strong negative responses when encountering reminders of the trauma, and an inability to discriminate between safe and dangerous cues and situations, often characterized as generalization of fear [9]. Thus, it is of utmost importance to investigate whether a brief intervention following trauma that either promotes or prevents sleep could have long-term clinical consequences. Given the contrasting findings of previous work, we cannot yet responsibly manipulate sleep after an actual traumatic event and must continue to study laboratory models with healthy participants and larger sample sizes.

2.2. Sleep and extinction recall

Even though some accounts argue that sleep immediately after a negative experience should be avoided, no one would argue that disturbed sleep has any positive consequences in the long run for when it comes to processing a negative experience. On the contrary, it has instead frequently been suggested that disturbed sleep is involved in maintaining the inability to process the event, perhaps through inhibiting the consolidation of safety

memories. Results from studies on ***extinction recall*** have been more convergent, and have showed that sleep, and especially REM sleep, increases extinction recall. Here the desired outcome is also much clearer, we want as much extinction recall as possible. An early study showed increased extinction recall in participants who had REM sleep during a nap as compared to those who did not [10]. This effect was however only present during late trials of the re-test, suggesting that perhaps REM sleep enabled additional safety learning rather than consolidated extinction learning. Other studies have shown REM sleep to be correlated with extinction recall [11], and that fragmented REM sleep during the post extinction learning night was associated with lower extinction recall [12*]. It is however difficult to know if REM sleep is the causal mechanism, or if more REM sleep is a marker of having experienced the conditioning as more aversive. Such an interpretation can be suggested based on studies finding that shock reactivity during conditioning was associated with decreased REM sleep [10], that not being able to learn the safety cue during conditioning was associated with more fragmented REM sleep [5], and that larger strength of the electric shocks made sleep more fragmented [13]. Because the above findings were correlative, a study that found reduced extinction recall by actively manipulating the amount of REM sleep through selective REM deprivation [14] is especially important because it addresses the question of causality. Another result indicating a role of REM sleep found increased extinction recall after late, but not after early sleep [4]. It should also be mentioned that three studies have not found any differences between a sleep and wake group when it comes to extinction recall [3, 12*, 15]. An additional study found that sleep decreased responses to a CS+U, without affecting responses to the CS− or the CS+E, [16]Results from a subsequent study however, suggested that this effect could have been produced by circadian factors [17].

2.3. Clinical applications

Several studies have attempted to apply the role of sleep in consolidating extinction learning to clinical settings. These studies have examined whether sleep might augment exposure therapy - a therapy for anxiety-related disorders that relies on extinction learning. Sleep has been found to consolidate the effects of exposure therapy for spider phobia [18], This was also found in another study that additionally found sleep to generalize these gains to a novel spider not seen before [19]. Such sleep dependent generalization effects could be of major clinical importance given that generalization of extinction learning is a major goal of exposure therapy for a variety of anxiety-related disorders as it allows therapeutic learning to influence encounters with a variety of feared stimuli outside the therapeutic context. One study did however not find any effects of sleep as compared to wake after exposure therapy on subsequent reactivity to spiders [20]. Yet another study compared 120-min post-exposure nap opportunities to wakefulness following two exposure sessions during a 5-session behavioral treatment for social anxiety disorder [21*]. Participants who napped showed a trend towards lower psychophysiological and cortisol responses to a social challenge re-test, but no greater change in a clinical assessment. Another potential clinical application comes from a study showing that reconsolidation blockade following reactivation of conditioned fear using propranolol required subsequent sleep in order to be expressed [22*].

Researchers have only recently begun to examine the relationship between impaired extinction learning and sleep in clinical groups. Straus et al. [23] repeated their previous

findings from healthy subjects [12*] in a PTSD sample and found that an inability to learn the safety cue (CS−) during conditioning was related to more fragmented REM sleep during subsequent sleep. There was, however, no relationship between post extinction learning REM sleep and extinction recall. Sleep disturbances have also been found to moderate the relationship between PTSD severity and reinstatement of fear (increased reactivity to the CS + following extinction after the subject receives un-signaled (not preceded by the CS+) shocks) [24]. Seo et al. [25*] found that individuals with primary insomnia showed a delayed fear extinction response, as evident by healthy controls showing a pattern of neutral activity at the end of the extinction learning phase that did not appear in those with primary insomnia until 24 h later.

Targeted memory reactivation studies have attempted to repeat cues (sounds or odors), that were present during extinction learning, during subsequent sleep, in order to reactivate the memory of extinction learning and enhance its consolidation. One study found that presenting such cues during sleep was more efficient for increasing fear extinction than repeating them during wakefulness [26]. However, two other studies found no differences between replaying cues during sleep or wake [20, 27], whereas another study found no differences between replaying the CS+ and the CS− during early or late sleep [28]. And lastly, one study repeating the CS+ during sleep in an attempt to produce *de novo* fear extinction, revealed no differences between a sleep and a wake group [15].

2.4. The impact of sleep prior to fear and extinction learning

Beyond the studies mentioned above about how reactivity during conditioning can affect subsequent sleep [5, 10], general sleep efficiency has previously been associated with extinction recall [29]. Thus, another important factor, that lately has been getting increased attention, is the role of sleep prior to fear and extinction learning. REM sleep following fear conditioning has been found to be negatively correlated with reactivity to the CS+E during extinction learning the next day [30], suggesting that REM may be important for the subsequent acquisition of extinction learning. Similarly, one study found that more REM sleep during the nights preceding fear conditioning resulted in decreased fear acquisition, suggesting that REM may also serve a protective function against acquiring exaggerated fear responses [31*].

Studies that have manipulated sleep prior to fear or extinction learning have reported contrasting results. Straus et al. [12*] found that sleep depriving participants during the night between fear conditioning and fear extinction learning did not impair their ability to acquire extinction learning, but that it did lower extinction recall one additional day later. However, no such impaired extinction recall was found in the group that were sleep deprived during the night between extinction and the re-test. Another study found that sleep deprivation prior to conditioning resulted in increased fear acquisition, and that these effects were still present during an extinction session one additional day later [32]. Lastly, one study found that partial sleep deprivation the night before conditioning reduced habituation, but that it did it so equally for all stimuli, and thus did not affect the differential fear acquisition [33].

3. Conclusion

As described above, the contrasting findings in the literature suggest that we still do not know what role sleep has in the aftermath of fear learning. Further, given the fact that aversive events also disrupt subsequent sleep, it is possible that good normal sleep would be beneficial, whereas the aroused sleep one would have after a traumatic experience would not. This should also be taken into consideration when attempting to determine the role of sleep in the aftermath of a negative experience. Further, if negative affect impairs sleep, and if impaired sleep hinders the consolidation of safety memories, this could create a vicious cycle where these two factors exacerbate each other [34]. An important task for future studies is to experimentally examine if improving sleep before and after exposure therapy improves the retention of therapeutic extinction. Further, sleep should be manipulated to see which factors have the greatest impact on outcomes. For example, one might increase REM sleep to see if it could enhance extinction recall. Correlating sleep with mood factors will also indicate to what extent sleep quality and architecture play a mechanistic role in extinction and exposure outcomes, or, alternatively, whether they represent trait markers for emotional processing in general. In summary, this emerging field holds great promise to inform us on how sleep might be leveraged to influence fear and safety learning and optimize mental health.

Given the current replication crisis in psychology, it should also be mentioned that recent papers [35,36] have warned about the lack of standardization when it comes to the procedures and analyses of fear conditioning paradigms. Because of this, it is possible that the number of significant findings within this field are exaggerated. This is especially important considering that studies have also analyzed sleep, and especially REM sleep, in different ways such as calculating time spent in REM, percentage of time spent in REM, REM efficiency or median splits. In the future, greater standardization will be needed to improve comparability between studies.

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Text box 1

Fear acquisition is defined as the difference in reactivity between the CS+ and the CS− during the conditioning phase (measured through subjective ratings, skin conductance responses, eye blink startle responses or neural activation; for readability, we will not go into detail about different measures of reactivity in this review).

Fear recall is defined as the difference in reactivity between the CS+ and the CS− during the re-test following a delay interval.

Extinction recall is most often defined as the difference in fear responses between the CS +E and the CS−, and sometimes as the decrease in responses to the CS+E at the re-test as compared to during the end of fear conditioning.

Generalization is when reactivity from conditioning is transferred to novel stimuli only presented during the re-test.

Rapid Eye Movement (REM) sleep is a sleep stage characterized by high cholinergic and low adrenergic tone, muscle paralysis, high activity in the hippocampus and the amygdala as well as rapid eye movements.

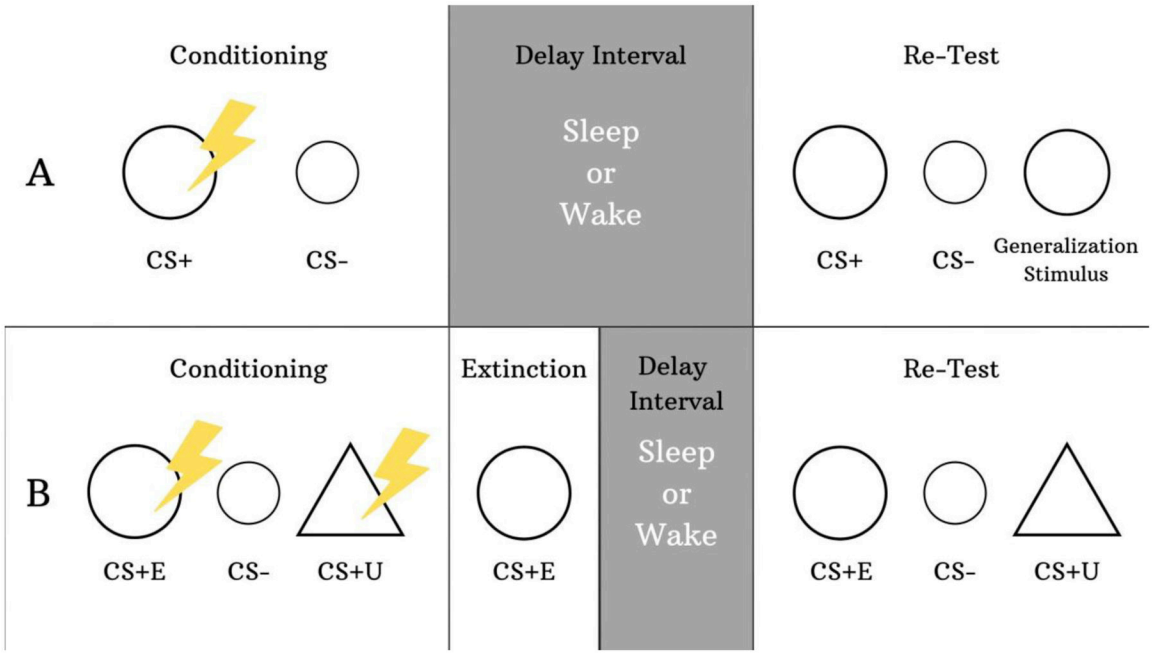

Figure 1.

A) Fear conditioning is the process in which a previously neutral stimulus (e.g. an image), is repeatedly paired with an aversive stimulus (e.g. an electric shock). With repeated pairings, the previously neutral stimulus will become associated with the aversive stimulus to a degree that it will start to elicit a fear response on its own, making it a conditioned stimulus (a CS +). These studies also include a stimulus that is never paired with the aversive stimulus, making it a safety stimulus (a CS−). By manipulating if participants spend the time between fear conditioning and re-exposure to the CS+ and the CS− asleep or awake, it is possible to study the role sleep has in consolidating fear and safety learning. In some studies, a stimulus that is in some aspect similar to the original CS+ is added during the re-test, to examine if sleep and wake differently generalizes the fear response from the CS+ to other, similar stimuli. **B)** If subsequently the CS+ is repeatedly showed without being paired with the aversive stimulus, a new safety memory, an extinction memory, is formed which decreases the reactivity to the CS+, making it an extinguished CS+ (a CS+E). This process is called fear extinction. These paradigms often also contain a second CS+ for which the fear is never extinguished, making it a CS+U.