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Conversion of short-term to long-term memory in the novel object recognition paradigm

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ABSTRACT

It is well-known that stress can significantly impact learning; however, whether this effect facilitates or impairs the resultant memory depends on the characteristics of the stressor. Investigation of these dynamics can be confounded by the role of the stressor in motivating performance in a task. Positing a cohesive model of the effect of stress on learning and memory necessitates elucidating the consequences of stressful stimuli independently from task-specific functions. Therefore, the goal of this study was to examine the effect of manipulating a task-independent stressor (elevated light level) on short-term and long-term memory in the novel object recognition paradigm. Short-term memory was elicited in both low light and high light conditions, but long-term memory specifically required high light conditions during the acquisition phase (familiarization trial) and was independent of the light level during retrieval (test trial). Additionally, long-term memory appeared to be independent of stress-mediated glucocorticoid release, as both low and high light produced similar levels of plasma corticosterone, which further did not correlate with subsequent memory performance. Finally, both short-term and long-term memory showed no savings between repeated experiments suggesting that this novel object recognition paradigm may be useful for longitudinal studies, particularly when investigating treatments to stabilize or enhance weak memories in neurodegenerative diseases or during age-related cognitive decline.

1. Introduction

In humans, many factors impact the ability to acquire, consolidate, or retrieve memories, including the attention, motivation, anxiety or stress of the subject during the relevant event or experience (McGaugh, 2013). In rodents, however, it is difficult to precisely define or measure these (and other) psychological constructs; instead investigators must often rely on the manipulation of an external variable (such as an environmental parameter) and the measurement of an indirect output (such as behavioral performance). To further complicate matters, the effect of altering external stimuli on learning and memory is not straight-forward: several distinct characteristics including the duration, intensity, and learning phase in which it occurs (for example, consolidation versus retrieval) can all affect whether the resulting memory is enhanced or degraded.

Emotional arousal due to stress has been extensively studied in rodents and thus represents a useful framework in which to examine the complex interplay between different factors of emotionally arousing stimuli. Interestingly, stress has been shown to result in both facilitation and impairment of memory (Bartolomucci, de Biurrun, Czeh, van Kampen, & Fuchs, 2002; Conrad, LeDoux, Magarinos, & McEwen, 1999; Diamond, Park, Heman, & Rose, 1999; Holscher, 1999; Luine, Martinez, Villegas, Magarinos, & McEwen, 1996; Luine, Villegas, Martinez, & McEwen, 1994; Mather, 2007; Miracle, Brace, Huyck, Singler, & Wellman, 2006; Nishimura, Endo, & Kimura, 1999; Sandi, Loscertales, & Guaza, 1997; Shors, 2001; Song, Che, Min-Wei, Murakami, & Matsumoto, 2006). Several recent reviews (Joels, Pu, Wiegert, Oitzl, & Krugers, 2006; Kim & Diamond, 2002; Sandi & Pinelo-Nava, 2007) have helped considerably in reconciling these seemingly contradictory results by summarizing important characteristics that need to be taken into account when evaluating the effect of stress on learning and memory. For example, stress differentially affects particular types of memory: stress has been shown to simultaneously facilitate memory for emotionally arousing events, but impair memory for neutral events (Payne et al., 2007). Likewise, when the stress is induced relative to the phase of learning is critical: stress experienced prior to acquisition has been shown to have no effect (Li et al., 2008) or to facilitate subsequent memory formation (Shors, Weiss, and Thompson, 1992)

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while stress experienced during retrieval often results in a memory deficit (de Quervain, Roozendaal, and McGaugh, 1998; Li et al., 2008). Finally, there is a complex relationship (often referred to as an "inverted-U-shape") between the intensity of a stressor and the effect on learning and memory: animals that experienced moderate stress (cooler water temperature) during spatial learning in the Morris water maze exhibited better memory than animals that experienced a less stressful condition (warmer water temperature) (Sandi et al., 1997). However, if the water temperature was lowered further (representing a more intense stressor), animals did not exhibit a corresponding enhancement of memory; in fact, memory was significantly impaired relative to the moderate stress group (Salehi, Cordero, & Sandi, 2010).

Exposure to bright light in an open area is thought to be stressful to rodents and produces anxiety-like behavior (Bert, Felicio, Fink, & Nasello, 2005); further, previous work has shown that altering light levels can disrupt learning and memory (Huang, Zhou, & Zhang, 2012; Pico & Davis, 1984; Roedel, Storch, Holsboer, & Ohl, 2006). However, we postulated that modulating light level may also be able to facilitate learning and memory, similar to the bidirectional effect observed with other stressors. In order to test this hypothesis, it was critical to choose a paradigm in which performance is not aversively motivated (for example, by shock delivery or water temperature, which are inherently stressful themselves). The novel object recognition paradigm is ideal for this purpose because it takes advantage of a rodent's intrinsic exploratory drive and, at least below some threshold, ambient light level does not significantly impair exploration (Bats et al., 2001). To perform this task, animals are first allowed to explore two identical objects during a familiarization trial. After a delay period (which can be varied to investigate short-term or long-term memory), they are exposed to one copy of the original object ("familiar") and a new object ("novel") in a test trial. Because rodents have an inherent preference for novelty, memory for the object from the familiarization trial is inferred if significantly more time is spent exploring the novel object relative to the familiar one (they must be able to remember the previously encountered familiar object to determine which object is "novel" during the test trial) (Bevins & Besheer, 2006; Dere, Huston, & De Souza Silva, 2007; Ennaceur, 2010).

Thus, by manipulating light levels during novel object recognition, we were able to examine the effect of modulating this emotionally arousing stimulus on learning and memory. We show that short-term memory could be reliably elicited regardless of light level, while long-term memory required elevated light levels during the familiarization trial and could not be elicited even with multiple familiarization sessions under low light conditions. Importantly, the light level during the test trial (when memory was being assessed) did not impact performance, suggesting that it was the formation of long-term memory (during the familiarization trial) that was critically dependent on the effects of elevated light. Interestingly, both low and high light conditions during familiarization produced significant elevations in plasma corticosterone concentration compared to baseline, but the formation of long-term memory did not correlate with corticosterone level. In combination with previous work, which reported memory impairments produced by modulating light levels (Huang, Zhou, & Zhang, 2012), our results demonstrate that light level can bidirectionally modulate learning and serve to strengthen the information encoded such that a weak, short-term memory is converted into a robust, long-term memory.

2. Materials and methods

2.1. Animals

Stock C57BL/6 mice were obtained from Taconic Farms (Cambridge City, IN). To eliminate potential sex-related confounds in the interpretation of our results, only male mice were used for these experiments. Mice were group-housed in cages of 3–5 animals, maintained on a 14:10-h light:dark cycle with *ad libitum* access to food and water. All experiments were conducted during the light phase (6 am - 8 pm) and the time of day (morning or afternoon/evening) was randomized so that there was no systematic bias with respect to experimental condition. All mice were 3-10 months old at the time of the experiments. Mice did not receive extensive handling or exposure to the training room prior to the start of each experiment. All procedures were performed in accordance with the University of Michigan Animal Care and Use Committee.

2.2. Novel object recognition

The arena used for all trials was a 17-gallon circular container made of white polyethylene, 42 cm high and 44.5 cm in diameter (Chem-Trainer, West Babylon, NY). The first day of each experiment consisted of 2–3 habituation trials (5 min each, 15–20 min apart) during which mice were exposed to the arena alone (no objects) in the training room. Twenty-four hours later, the experimental trials began, which consisted of a familiarization phase and a test phase separated by a variable delay period. During the familiarization phase (which consisted of 1 or 3 individual trials, as indicated), mice were placed in the arena which contained two copies of an object and allowed to freely explore (5 min per trial). After either a short (2 min) or long (24 h) delay period, a test trial (5 min) was conducted; mice were returned to the arena which contained one of the original objects ("familiar") and a new, different object ("novel"). The objects used in all experiments were custom made in-house from LEGOs® (see Fig. 1). These objects had been previously validated to ensure they would elicit substantial exploration (at least 30 s, on average) and that there was no inherent preference for either object. The object assignments (familiar or novel) and locations (left or right side of the arena) were counterbalanced within each experiment, as well as within subject for subsequent experiments. Objects were placed in the center of the arena approximately 10 cm from the arena wall and held in place with adhesive tack (such as Blu-Tack®). The arena and objects were cleaned between each trial with 70% ethanol. For all trials, background white noise (approximately 66 dB) was provided by an air purifier. The room was illuminated by indirect white light, the level of which (measured in the center of the arena) was defined as "low" (range: 2.7–3.3 lux) or "high" (range: 20.9–22.2 lux) as indicated for each experiment (all habituation trials were always conducted in low light). It should be noted here that these are relative terms; ambient light levels in our animal housing room are typically 400–500 lux. Therefore, the "high" light level in our experiments should be considered moderate in a general context, and the terms "low" or ~3 lux and "high" or ~21 lux are used for clarity in the text.

2.2.1. Corticosterone assay

In a separate experiment, corticosterone (CORT) levels were also measured in mice that performed novel object recognition. Because CORT levels are generally lowest at the beginning of the light phase (Malisch, Breuner, Gomes, Chappell, & Garland, 2008; Ottenweller, Meier, Russo, & Frenzke, 1979), all experiments involving CORT (see Fig. 9) were performed from 6 am to 10 am. Blood samples were collected from each mouse (via tail-vein bleed) at the following points: (1) 2 weeks prior to the novel object recognition experiment (to establish a baseline level); and (2) 20 min after the familiarization trial. The 20-min post-familiarization time point was selected because pilot studies indicated that CORT levels peaked approximately 15–30 min after the "stressful" experience (being placed in the arena with the objects during the