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The amygdala and prioritization of declarative memories

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Abstract

The present review highlights results from recent studies that delivered brief electrical stimulation to the basolateral complex of the amygdala in rats to reveal its capacity to prioritize declarative memories on a moment-to-moment basis even after the moment has passed. The results indicate that this memory enhancement depends on the hippocampus and elicits intrahippocampal gamma synchrony that possibly corresponds with sharpened hippocampal spike-timing dependent plasticity. These recent findings are discussed in relation to past studies of emotional memory in rodents and humans.

Keywords

amygdala; memory; consolidation; emotion; stimulation

The neuroscience of emotion has focused on the amygdala, a heterogeneous cluster of forebrain nuclei that show a considerable degree of conservation across mammals (Swanson & Petrovich, 1998). The amygdala is one of the most widely connected regions of the brain, and one common view is that, through this extensive network of inputs and outputs, the amygdala plays a fundamental role in learning and leveraging the affective salience of stimuli (Cunningham & Brosch, 2012; Morrison & Salzman, 2010; Pessoa, 2010). The topic of the present review, an important subset of this broader function, is the role of the amygdala in prioritizing the type of everyday memory for facts and events typically termed declarative memory.

Emotional memory enhancement in humans and the role of the amygdala

Events and material that elicit emotional arousal are often remembered better than information learned without arousal (Cahill & McGaugh, 1998; Hamann, 2001). The effects of arousal on memory are, however, complicated and variable (Bennion, Ford, Murray, & Kensinger, 2013). A large body of work has revealed that a number of factors can influence this process, including the level of arousal, the valence of the emotion, and the sex of the participant (LaBar & Cabeza, 2006). One important understanding to emerge from this work is that, apart from directly boosting memory processes, emotional arousal can marshal many other cognitive and hormonal resources to improve subsequent memory, resources related to vigilance, perception, attention, and working memory (Phelps & Ledoux, 2005). Further,

emotional and neutral stimuli can differ along dimensions orthogonal to affect, such as unusualness or interrelatedness, and these differences inherent to the stimuli can also influence memory (Talmi, 2013). Moreover, emotional memories can also differ in one's subjective confidence in the accuracy of the remembrance or in the relative extent to which foreground stimuli or background contextual elements are remembered (Bennion et al., 2013). Thus, when it comes to emotional memory, the full story goes beyond both emotion and memory.

Nevertheless, there is good evidence that emotional arousal can give memory processes a direct boost, even after the event has transpired. For example, the effect of emotion on memory can unfold over time after the incident and in some cases be augmented by sleep (Payne, Chambers, & Kensinger, 2012). As another example, watching a short video of either a comedy skit or oral surgery up to 30 minutes after reading a list of neutral words led to improved memory for those words one week later (Nielson & Powless, 2007). Further, a mild shock delivered to participants while viewing neutral pictures of either animals or tools improved subsequent memory for previously viewed images of the same animal or tool category (Dunsmoor, Murty, Davachi, & Phelps, 2015). These results suggest that one large target of emotion is memory consolidation, which, stated most generally, refers to post-encoding processes during which the memory trace is buttressed against degradation.

Functional brain imaging studies and results from patients with brain damage have shown the amygdala to be central to the emotional benefit to memory. For example, early PET studies indicated that activity in the amygdala for emotionally-arousing material but not neutral material correlated with subsequent memory (Cahill et al., 1996; Hamann, Ely, Grafton, & Kilts, 1999). In addition, a patient with damage to the amygdala showed normal declarative memory for neutral material but no additional boost for emotional material (Adolphs, Cahill, Schul, & Babinsky, 1997). These results contrast with the finding that patients with damage to the adjacent hippocampus that spares the amygdala show a more general impairment in declarative memory (Rempel-clower, Zola, Squire, & Amaral, 1996). Thus, the hippocampus (along with entorhinal, perirhinal, and parahippocampal cortices) is essential for forming declarative memory generally, whereas the amygdala is engaged more specifically for modulating declarative memories formed within an emotional context. The amygdala projects directly to the hippocampus, entorhinal cortex, and perirhinal cortex (Petrovich, Canteras, & Swanson, 2001), and these projections are likely key to the amygdala's capacity to influence emotional declarative memory consolidation, even if the interactions between the hippocampus and amygdala represent only one route by which arousal can benefit memory.

The amygdala and modulation of memory consolidation in rodents

Much of the research on the role of the amygdala in emotional memory has been conducted in rodents and has focused specifically on the basolateral complex of the amygdala (BLA). A considerable amount of this work has highlighted the role of the BLA in acquiring nondeclarative positive or negative dispositions towards previously neutral stimuli, an approach frequently exemplified by tone-shock conditioning that engages the BLA to associate the tone with threat (Ledoux, 2014). A separate but related line of work has sought

to understand how activation of the BLA can influence downstream processes in other brain regions to improve declarative memory for an emotionally arousing incident (McGaugh, 2013). For example, optogenetically activating the BLA in rats after inhibitory avoidance training led to improved one-day memory performance for this type of aversive learning (Huff, Miller, Deisseroth, Moorman, & LaLumiere, 2013). More broadly, we now understand that the amygdala both contributes to the release of epinephrine and glucocorticoids from the adrenal glands and is in turn influenced, directly and indirectly, by those same hormones (McGaugh, 2004).

Much of the research regarding the role of the BLA in modulating memory in downstream structures has involved pharmacological measurements or manipulations of the BLA. From this large body of work, several findings are worth highlighting. First, emotionally arousing experiences lead to increased levels of several modulatory neurotransmitters in the BLA, including acetylcholine and norepinephrine (NE) (McGaugh, 2004). The level of increase of NE in particular correlates with subsequent memory for the event, and blocking the action of NE in the BLA impairs this memory (McIntyre, Power, Roozendaal, & McGaugh, 2003). Second, pharmacologically activating the BLA by directly infusing small amounts of NE, even after the end of an emotionally arousing event, can improve subsequent memory for the event (McGaugh & Roozendaal, 2009). Third, infusing NE into the BLA after a study session can enhance memory even when the material is not overtly emotional (Roozendaal, Castello, Vedana, Barseganyan, & McGaugh, 2008). Fourth, infusion of NE in the amygdala during a memory task resulted in increased expression in the hippocampus of proteins that have been associated with cellular processes related to synaptic plasticity and memory consolidation (McReynolds, Anderson, Donowho, & McIntyre, 2014). Although the role of activating the BLA is perhaps better understood for NE than it is for other neurotransmitters, local infusion of several other drugs can also activate the BLA and recreate some of the above findings (McGaugh & Roozendaal, 2009). Taken together, the data indicate that pharmacological activation of the BLA can boost the memory of a recent experience even if that event was not emotional and can modulate cellular consolidation processes in the hippocampus.

A fundamental understanding to emerge from studies using post-encoding pharmacological activation of the BLA is that its role in prioritizing affective stimuli does not end with the disappearance of the stimuli. Nevertheless, as activation of the BLA in these studies lasts for up to an hour or more and comes after the end of an entire study period, an important question is then how some memories can be prioritized over others for long-term storage. A key question is thus how the BLA can modulate declarative memory consolidation at a time scale short enough to benefit memories of only select moments but not others.

Prioritization of declarative memory by brief electrical stimulation of the amygdala

Several recent experiments have sought to address this question by delivering very brief (1 s) bouts of pulsed electrical current at very low levels (20 μ A) directly to the BLA as rats were given the opportunity to explore and form memories of dozens of different neutral toy-like

objects (Bass & Manns, 2015; Bass, Nizam, Partain, Wang, & Manns, 2014; Bass, Partain, & Manns, 2012). Similar to the studies using pharmacological activation of the BLA, the electrical stimulation was delivered to the BLA only after object exploration ended. However, unlike the prior studies, the electrical stimulation was delivered immediately, within 1 s after cessation of exploration, and was targeted to only a subset of the dozens of object encounters that occurred within seconds or minutes of one another. The question was whether temporally precise activation of the BLA, even when the stimulation was delivered after exploration ended, could prioritize memories on a moment-to-moment basis.

The first of these studies (Bass et al., 2012) found that stimulation of the BLA at the offset of initial object exploration led to markedly improved memory for objects when memory was tested a day later. Indeed, rats showed almost no memory for the control objects by this point but showed very good memory for the objects for which the initial encounters had been followed by BLA stimulation. These results on the one-day test contrasted with results obtained in the same experiment when memory was tested immediately after the end of the study session. On the immediate test, rats showed equally good memory for objects regardless of whether the initial exploration was followed by BLA stimulation, paralleling earlier findings that highlighted the role of the BLA in prolonged processes of consolidation (Roosendaal et al., 2008). Additionally, because the memory task was based on rats' spontaneous object exploration, the lack of an effect on the immediate test also indicated that BLA stimulation did not alter rats' tendency to explore objects per se, suggesting that the influence on one-day memory for the objects was not tied to altering dispositions towards the objects. The same pattern of memory performance (unaffected immediate memory but improved one-day memory) was replicated twice in two subsequent studies (Bass & Manns, 2015; Bass et al., 2014). Figure 1 shows the combined memory performance from all three experiments and indicates that the BLA-mediated memory enhancement was robust, reliable, and specific to the one-day test.

These recent experiments also provided important information regarding the role of the hippocampus in BLA-mediated enhancement of declarative memory. When muscimol, a GABA_A agonist, was infused bilaterally in order to inactivate the hippocampus temporarily during the study session, the beneficial memory effect of BLA stimulation observed one day later was eliminated (Bass et al., 2014). In a subsequent study (Bass & Manns, 2015), stimulation of the BLA elicited synchronization of neuronal oscillations in the hippocampus in the slow gamma frequency range (approximately 30-55 Hz), a frequency range of hippocampal oscillations that has been previously associated with good memory in other experiments not involving amygdala stimulation (Trimper, Stefanescu, & Manns, 2014). Throughout the brain, neuronal oscillations provide rhythms that are thought to be important for orchestrating the precise timing of action potentials relative to the membrane state of target post-synaptic neurons (Buzsáki, Anastassiou, & Koch, 2012; Fell & Axmacher, 2011). With respect to the hippocampus, this precise timing is likely needed to initiate most effectively the molecular events that represent the type of cellular consolidation processes that unfold over the course of a day and bolster a newly formed memory trace (Alberini & Kandel, 2015; Jutras & Buffalo, 2010). Thus, one major avenue by which BLA activation influences memory consolidation for specific object encounters is likely by enhancing the synchrony of slow gamma oscillations in the hippocampus, which in turn promotes the

cellular consolidation processes for those particular memories. Indeed, BLA stimulation was associated with patterns of hippocampal spiking that reflected the recent object encounters (Bass & Manns, 2015). The results extend the previous findings by highlighting the capacity of the BLA to prioritize memories on a moment-to-moment basis even after the moment has passed and suggest that one route is by regulating spike-timing dependent plasticity in the hippocampus across the most recently active synapses.

Nevertheless, much is still unknown. For example, it is unclear how activation of the BLA leads to increased gamma synchrony in the hippocampus. Multiple pathways and mechanisms are possible, including engagement of oscillatory states in the hippocampus through direct projections from the BLA or through indirect projections via the perirhinal and entorhinal cortices (de Curtis & Pare, 2004). A related question is how any of these putative transient effects would be propagated in subsequent hours and whether brain states during sleep play an important role. Another important question is whether post-encoding activation of the BLA influences memory consolidation in such a way that the consolidated memories differ from other strong but neutral memories in terms of confidence in the memory or in terms of relative enhancement of foreground items versus background contextual elements.

A broader question is how BLA-mediated modulation of memory consolidation in the hippocampus fits into the larger role of the amygdala in learning and leveraging the affective salience of stimuli. Direct activation of the BLA after new declarative memories have been acquired can rather narrowly influence the retention of those memories. Such reductionism is important for tracking down the details of this endogenous mechanism of memory enhancement. However, in everyday emotional events, the BLA engages a wide set of brain regions to capitalize on the arousal both during and after the event. Indeed, several ideas have been proposed to suggest that the emotionality at the time of encoding becomes a key part of the memory rather than just a transient influence (Bergado, Lucas, Richter-Levin, 2011; Yonelinas and Ritchey, 2015). A full understanding of how the amygdala helps to identify important information and how it wields its extensive connections to capitalize on this affective salience more broadly will be needed to fully appreciate how the amygdala prioritizes declarative memory consolidation more specifically.

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Recommended Reading

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Figure 1.

Memory performance on a novel object recognition memory task on a test of half the objects given immediately after the initial study session and a test for the other half given one day later. Results are shown for objects for which the offset of initial exploration during the study phase was immediately followed by stimulation of the BLA and for objects for which initial exploration was not followed by stimulation. Performance is plotted as a discrimination index that represents the ratio of time spent exploring novel and repeated objects, which is used to infer memory for the repeated objects. A discrimination index of

0.50 (dashed line) represents chance performance, and a discrimination index of 0.65 (a 2:1 ratio of novel:repeated object exploration) is often considered to be near the upper limit of memory performance for the repeated objects on the task. Error bars show SEM. Data are combined from Bass et al., 2012 (n=9), Bass et al., 2014 (n=9; saline condition), and Bass and Manns, 2015 (n=7). Performance on the immediate test is nearly the same for both stimulation conditions. On the one-day test, memory performance is markedly higher for objects for which the initial exploration during the study phase was followed by stimulation of the BLA ($t(24) = 3.59$; $p = 0.001$; 95% confidence interval of the difference = 0.031 to 0.115).