Neurobiology of Learning and Memory xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

Review

How the amygdala affects emotional memory by altering brain network properties

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ARTICLE INFO

Article history:
Available online xxxx

Keywords:
Amygdala
Emotional memory
Stress hormones
Memory consolidation
Connectivity

ABSTRACT

The amygdala has long been known to play a key role in supporting memory for emotionally arousing experiences. For example, classical fear conditioning depends on neural plasticity within this anterior medial temporal lobe region. Beneficial effects of emotional arousal on memory, however, are not restricted to simple associative learning. Our recollection of emotional experiences often includes rich representations of, e.g., spatiotemporal context, visceral states, and stimulus–response associations. Critically, such memory features are known to bear heavily on regions elsewhere in the brain. These observations led to the modulation account of amygdala function, which postulates that amygdala activation enhances memory consolidation by facilitating neural plasticity and information storage processes in its target regions. Rodent work in past decades has identified the most important brain regions and neurochemical processes involved in these modulatory actions, and neuropsychological and neuroimaging work in humans has produced a large body of convergent data. Importantly, recent methodological developments make it increasingly realistic to monitor neural interactions underlying such modulatory effects as they unfold. For instance, functional connectivity network modeling in humans has demonstrated how information exchanges between the amygdala and specific target regions occur within the context of large-scale neural network interactions. Furthermore, electrophysiological and optogenetic techniques in rodents are beginning to make it possible to quantify and even manipulate such interactions with millisecond precision. In this paper we will discuss that these developments will likely lead to an updated view of the amygdala as a critical nexus within large-scale networks supporting different aspects of memory processing for emotionally arousing experiences.

1. Introduction

Stressful and emotionally arousing experiences are preferentially retained in memory (Joëls, Fernández, & Roozendaal, 2011; Schacter, 1999). It has long been known that the amygdala, an anterior medial temporal lobe structure, plays a pivotal role in this usually highly adaptive phenomenon. The notion that the amygdala is involved in affective processing dates back to the classic report by Klüver and Bucy (1937) on the effects of temporal lobectomy in rhesus monkeys. Bilateral lesions of this region were shown to result in striking behavioral changes, including visual agnosia, dietary changes, and hypersexuality, but also profound alterations in affective behaviors, including tameness and loss of fear. Further investigations into these effects by Weiskrantz in the 1950s demonstrated that these affective changes were largely due to anteromedial temporal lobe lesions, particularly to the amygdala (Weiskrantz, 1956). Weiskrantz' work also demonstrated that amygdala lesions not only block the expression of conditioned fear, but also impair new fear learning. This observation set the stage for a line of research into the role of the amygdala in emotional memory that now spans multiple decades (McGaugh & Roozendaal, 2002; Phelps & LeDoux, 2005; Roozendaal, McEwen, & Chattarji, 2009). Initially, this research focused on the amygdala proper as a storage site for associations underlying fear memory (Davis & Whalen, 2000; LeDoux, 2000). For instance, it was shown that fear learning depends on the induction of neural plasticity within the basolateral complex of the amygdala (BLA) (Miserendino, Sananes, Melia, & Davis,

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http://dx.doi.org/10.1016/j.nlm.2014.02.005
1074-7427/

1990; Rogan, Stäubli, & LeDoux, 1997). These findings led to the view that the BLA might be a crucial site where sensory input converges and synaptic plasticity can produce lasting changes in emotional responses to environmental stimuli.

However, the beneficial effects of emotional arousal on memory extend well beyond associative fear learning. Recollection of emotional experiences typically includes not only representations of sensory cues, but, for example, also of spatial and temporal context in which these have been encountered (Christianson, 1992; Diamond, Campbell, Park, Halonen, & Zoladz, 2007; Phelps, 2004; Sandi & Pinelo-Nava, 2007). Importantly, such types of declarative memory rely heavily on neural systems elsewhere in the brain (Bird & Burgess, 2008; Henke, 2010). This notion has been corroborated by an extensive body of evidence documenting beneficial effects of stress hormones and neurotransmitters released during emotionally arousing experiences on various types of memory, both in rodents (McGaugh, 1989) and in humans (Lupien, Maheu, Tu, Fiocco, & Schramek, 2007; Schwabe, Joëls, Roozendaal, Wolf, & Oitzl, 2012). These developments led to the proposal that the amygdala contributes to enhancement of memory for emotional events primarily by integrating these neuromodulatory influences and modulating mnemonic activity and synaptic plasticity in other brain regions (McGaugh & Roozendaal, 2002; Roozendaal, McEwen et al., 2009). Research into the role of the amygdala in influencing memory consolidation processes in other memory systems was pioneered by James L. McGaugh and colleagues. However, this *modulation hypothesis* of amygdala function can historically be traced back to Ralph W. Gerard, who hypothesized already many years before the first experiments were performed that amygdalar nuclei could "modify the ease and completeness of experience fixation even if the nuclei were not themselves the loci of engrams" (Gerard, 1961).

As we will address below, the modulation hypothesis has received wide empirical support over the years. Rodent studies have utilized pharmacological manipulations, selective lesions and immediate-early gene activation to delineate the relevant structures, pathways and neurochemical processes. This work has dovetailed tightly with behavioral, psychopharmacological, neuropsychological, and neuroimaging studies in humans. However, more recent methodological developments make it increasingly feasible to monitor neural activity in real-time, and thus to explore how information is processed and exchanged between brain regions. For instance, the rapid proliferation of techniques for functional connectivity network modeling in humans using functional magnetic resonance imaging (fMRI) has made it possible to study interactions within large-scale neural systems in the human brain (Raichle, 2009). Findings gathered using these techniques have generated novel insights into how brain regions implicated in different types of memory are part of distinct large-scale connectivity networks (Ranganath & Ritchey, 2012). As explained below, these findings yield important heuristics for translation back to basic neuroscience, which offers the technology to investigate these processes more mechanistically and in more spatial and temporal detail. For instance, *in vivo* electrophysiological techniques in rodents now make it possible to simultaneously record activity of neuronal ensembles distributed across different brain regions during different phases of memory processing (Buzsáki, 2004), while optogenetic techniques allow manipulations of specific neural connections with millisecond precision (Boyden, Zhang, Bamberg, Nagel, & Deisseroth, 2005; Tye et al., 2011). Future application of these techniques to the amygdala and its many efferent connections will lead to a sophisticated understanding of how the amygdala engages stress hormone and neurotransmitter systems to modulate large-scale network properties and influence distant neural processes underlying the formation and consolidation of memory for emotionally arousing experiences.

2. Role of the amygdala in memory modulation

During an emotionally arousing episode, stress hormones (epinephrine and glucocorticoids) are secreted from the adrenal glands and several neurotransmitters and neuropeptides are released in the brain (Joëls & Baram, 2009). The amygdala plays a critical role in integrating these various neuromodulatory influences on memory (McGaugh, 1989, 2004). The modulation hypothesis proposes that during and shortly after an emotionally arousing experience, the amygdala engages stress-related hormones and neurotransmitters to enhance the consolidation and storage of memory within other parts of the brain. Studies performed since the 1970s have produced a wealth of convergent data supporting this notion. Gold and van Buskirk (1975) were the first to report that systemic post-learning injection of the adrenomedullary hormone epinephrine enhances long-term retention of inhibitory avoidance training. The epinephrine effect was both dose-dependent and time-dependent. Memory enhancement was greatest when epinephrine was administered shortly after training (Gold & Van Buskirk, 1975). Epinephrine-induced memory enhancement has now been extended to many other types of training in rodents (Costa-Miserachs, Portell-Cortés, Aldavert-Vera, Torras-García, & Morgado-Bernal, 1994; Introini-Collison & McGaugh, 1986; Sternberg, Isaacs, Gold, & McGaugh, 1985) as well as declarative memory in humans (Cahill & Alkire, 2003). Similar findings were obtained, for example, with post-learning elevations of adrenocortical glucocorticoid hormones in both rodents (Cottrell & Nakajima, 1977; Hui et al., 2004; Okuda, Roozendaal, & McGaugh, 2004; Roozendaal & McGaugh, 1996; Zorawski & Killcross, 2002) and humans (van Marle, Hermans, Qin, Overeem, & Fernández, 2013; Wilhelm, Wagner, & Born, 2011). However, these stress hormones appear to affect memory consolidation only for emotionally arousing experiences in the presence of arousal-induced noradrenergic activity (Borrell, de Kloet, & Bohus, 1984; Borrell, de Kloet, Versteeg, & Bohus, 1983; Liang, Juler, & McGaugh, 1986; Okuda et al., 2004; Roozendaal, Carmi, & McGaugh, 1996; Roozendaal, Okuda, van der Zee, & McGaugh, 2006). A similar dependency on concurrent noradrenergic activity was found for other memory-enhancing compounds such as the opiate receptor antagonist naloxone (Izquierdo & Graudenz, 1980), corticotropin-releasing factor (CRF) (Lee, Lee, Wang, & Lin, 1993), and cannabinoid compounds (Atsak, Roozendaal, & Campolongo, 2012). As we will discuss below, extensive evidence indicates that the effects of various stress-related neurochemical changes converge onto arousal-induced activation of noradrenergic transmission within the amygdala, which in turn interacts with other brain regions in regulating the consolidation of different types of memory. Although in this paper we will mainly focus on the role of the amygdala in regulating the encoding and consolidation of memory, there exists now compelling evidence that amygdala activity, via its interactions with other brain regions, is also crucially involved in regulating stress hormone and emotional arousal effects on other aspects of memory processing such as memory retrieval, memory extinction, and working memory (Roozendaal, Hahn, Nathan, de Quervain, & McGaugh, 2004; Roozendaal, McReynolds, & McGaugh, 2004).

2.1. Evidence for a modulatory role of the amygdala in rodents

Findings of experiments by Kesner and Ellis (Kesner & Ellis, 1983; Ellis & Kesner, 1981) and Gallagher (Gallagher, Kapp, Pascoe, & Rapp, 1981) were the first to suggest that the noradrenergic system of the amygdala is involved in influencing memory consolidation. A ß-adrenoceptor antagonist administered into the amygdala post-training was shown to impair memory, while concurrent infusion of norepinephrine blocked this memory impairment

Please cite this article in press as: Hermans, E. J., et al. How the amygdala affects emotional memory by altering brain network properties. *Neurobiology of Learning and Memory* (2014), http://dx.doi.org/10.1016/j.nlm.2014.02.005