Running Head: Role of the amygdala in long term memory

What is the Role of the Amygdala in Long Term Memory?

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The amygdala is well renowned for its role in memory, particularly during fear conditioning. During Pavlovian fear conditioning, the lateral amygdala receives input from both the conditioned stimulus (CS) and the unconditioned stimulus (US) and is thought to be the site of plasticity for the association between the CS and the US (Phelps, 2009). The amygdala also becomes active in humans during exposure to strong aversive odorants, suggesting that the amygdala makes use of the transduction of negative odorants in some way as to lead to the consolidation of fear memories, catalyzing the retention of experience surrounding the exposure (Zald; Pardo, 1997). The amygdala also responds to identify reward representations, working with the orbitofrontal cortex to help promote behavior that can result in rewards (Gottfried et al., 2003). The amygdala, therefore, seems pivotal in labeling the retention of past experiences with an emotional tag, supplying the organism with an emotional context in which to interpret the memory, and with any luck, an adaptive advantage.

However, the amygdala also seems to have a role in the formation of long term memory; meaning that not only do the various amygdalar nuclei tag memories, they also seem to be part of a process that reinforces lasting memory retention. Recent fMRI analysis has found that localized metabolic increases in the amygdala during moments of insight can be used as a predictive measure for which solutions derived from insight will be remembered one week after the exercise (Rubin et al. 2011). In this study the insight task utilized camouflaged images, which were subsequently revealed (allowing for a moment of insight), but the experiment coordinators went to great lengths to ensure that the images themselves were neutral, i.e. nothing grotesque or arousing. This is surprising, because the amygdala was not obviously tagging the learning experience (the insight) with emotion, in fact many of the

participants only reported mild feelings of bemusement or indifference during the task. Depending upon interpretation, the amygdala may have performed one or both of the following roles; the very use of the amygdala meant that the insight moment was a subconscious emotional event, or/and the amygdala was performing a non-emotion based task. Regardless of the interpretation, the amygdala clearly has a role in long term memory retention. An interesting follow-up to the Rubin study would be to investigate whether or not the amygdala became active during the testing of long term memory retention, i.e. is there increased amygdala activation during exposure to the camouflaged images that one week ago elicited an increased response during insight.

In order to figure out the molecular mechanisms involved in memory retention with regards to the amygdala, Parsons et al. (2006) sought to determine if the molecular mechanisms for fear memory consolidation (the initial storing of memory) was the same as the mechanisms for memory reconsolidation (the recalling and further consolidation of memory) in the rat. The team found that fear memory consolidation required mRNA transcription and translation in the amygdala, but reconsolidation only required translation; the reason being that the mRNA transcript for the consolidation protein was still present in the tissue, so blocking transcription at this stage had no effect. This means that memory reconsolidation is not dependent on transcription, unlike consolidation; a reduction in the biochemistry needed for reconsolidation is of course beneficial for long term memory retention. The very presence of the mRNA transcripts in the cytoplasm is crucial for consolidation and reconsolidation, and so

should be considered an important part of the long term memory process. In fact if neurons in the amygdala are prevented from making new mRNA after conditioning, then no new memories are formed (Kwapis et al. 2009). The activation noted in the Rubin study could be the increased transcription of memory enhancing proteins. Parsons et al. also raise the point that the neuro-mechanics of reconsolidation must be similar to extinction training, which is the uncoupling of a US and a CS to the point where the CS predicts the absence of the US; at a particular site (probably in the amygdala), a memory can either be reconsolidated or unassociated (extinction), depending on the input and biochemical environment. A protein synthesis inhibitor infused into the amygdala before a short exposure to a CS will lead to greater chances for extinction, whereas when the infusion is given before an extended period of exposure to the CS, the chances of extinction become low (Pedreira; Maldonado, 2003).

On top of transcriptional activation and protein synthesis during memory retention, there are also changes in the motility and morphology of synapses after a learning event (Maguschak; Ressler, 2008). According to this study, one of the proteins responsible for these structural changes is β-catenin. Mice that were engineered without the Ctnnb1 gene (β-catenin) were unable to process newly formed fear memories for long term retention; this was observed in the amygdala, and so it was deemed that this protein is not necessary for memory acquisition, but is needed for retention, and so the structural differences it causes at the synapse by interacting with the cadherins (molecules that help to hold tissue together) appears necessary for long term memory formation, at least for fear memories. In this study it was

found that the affinity of cadherins for β-catenin weakened during acquisition, but strengthened during consolidation, suggesting that the relationship between the two molecules is contingent with the changes in plasticity of the neurons during acquisition and learning; once the learning has taken place, therefore, β-catenin helps to stabilize neuronal structure, which must play a role in preserving the memory by stabilizing the neuronal circuit.

Further evidence for synaptic plasticity in the amygdala is given by Sigurðsson et al. (2010) as they investigated thalamic and cortical inputs to the lateral amygdala (LA) in rats. By using paired pulse stimulation and by inserting stimulating electrodes into the left medial thalamic nucleus and the left TE3 area of the auditory cortex, and by placing a recording electrode into the lateral amygdala, the team was able to investigate levels of LTP in the left LA of the rat. Input from the cortex more readily resulted in LTP at the LA than input from the thalamus. The authors conclude that input to the amygdala from these two parts of the auditory systems might play different roles in emotional memory, which is interesting, given that both these areas, which handle auditory information, are feeding into the same specific limbic structure. The input from the cortex seems to be better able to depolarize the neurons in the LA, which no doubt accounts for the increased LTP; could this suggest that sensory information coming from the cortex has a higher chance of being remembered? To find highly localized function within such a tiny section of the brain would make planning an experiment exceedingly difficult, but discovering the nature of the information coming from both of these auditory areas would help shed light on the functional significance of their respective inputs to the lateral amygdala.

Stress seems to have an effect on memory consolidation; the activation of glucocorticoid receptors (which are relatively abundant in the basolateral amygdala), enhances consolidation of emotionally arousing tasks in rats (Roozendaal; McGaugh, 1997). This does not seem very surprising, as stressful or traumatic events due tend to get remembered over neutral memories, and so the presence of stress hormone receptors in the basolateral amygdala appears quite natural. Jin et al. (2007) wanted to take this study further and see if glucocorticoid receptors were necessary for reconsolidation with auditory fear memories. After conditioning rats with a prolonged tone accompanied by a foot shock, the rats were later tested for successful association, which had occurred in all instances. Immediately after the tone, a group of rats received the glucocorticoid antagonist RU486. High doses of this resulted in a diminished freezing time to future tone activations, suggesting the reconsolidation of the fear memory had been inhibited by RU486. So stress, even though potentially devastating to one's health, does play a key role in fear memorization AND making sure that the memory is lasting.

Clearly the amygdala is involved during memory consolidation and reconsolidation, and there are high levels of plasticity depending upon the saliency of the memory, but despite these activities, what is the amygdala doing in conjunction with other memory areas of the limbic system? Cahill and McGaugh (1993) found that by injecting NMDA into the rat amygdala, the expression of c-fos was increased in both the hippocampus and the caudate-putamen (CP). As c-fos is an indicator of increased neural activity, infusing a glutamate agonist into the amygdala clearly causes increased activation in both the CP and the hippocampus. Packard and Teather

(1998) examined the modulatory inputs that the amygdala had on the hippocampus and the CP by using infusions of lidocaine into the hippocampus or CP, while simultaneously infusing amphetamines into the amygdala. They had previously found that lidocaine nullifies the effects of the hippocampus and the CP, and when amphetamines are infused into the amygdala it aids memory retention in rats when they are presented with the hidden platform test in the Morris Water Maze. When amphetamines were simultaneously infused into the amygdala along with an infusion of lidocaine into *either* the hippocampus or the CP, the memories of the rats after the training exercise were impaired (Packard; Teather, 1998). This suggests that in order for there to be successful spatial memory retention, the hippocampus and the CP must receive input from the amygdala.

However, this seems somewhat paradoxical, because the amygdala and the hippocampus appear to serve in two different types of memory acquisition; the hippocampus is involved in spatial memory, and the amygdala is involved with making associations between emotions and discrete stimuli (Rutsuko et al. 2006). According to Packard and Teather it is possible that even though the amygdala and the hippocampus appear responsible for independent memory systems, the hippocampus still appears to have a functional reliance on the amygdala. To investigate this phenomenon, Rutsuko et al. investigated appetitive conditioning in a Y maze, where the performance of rats was measured after receiving lesions to the hippocampus or the amygdala. The type of appetitive conditioning used was conditioned place preference (CPP), which the authors assumed would be a task that relied heavily on the hippocampus due to the spatial dimension, yet paradoxically they explain that in previous studies, lesions to the amygdala have a greater impact on CPP. The team found that in a CPP

test with no landmarks to guide behavior, the task primarily relied on the hippocampus and the task was even enhanced when the rats had been given a basolateral amgydalarectomy. However, they found that when a distinct cue was used during the conditioning, then the task became very reliant on the basolateral amygdala. From this experiment they conclude that the hippocampus and the amygdala compete for control over appetitive behavior. This is very interesting because it sets the amygdala and hippocampus up on a spectrum, whereby conditioning that takes place over the course of a lifetime is being dissected and evaluated by these two different areas and activation occurs when the conditioning meets certain criteria. If the rats with the amygdalarectomy demonstrate enhanced performance in the contextual (cue-absent) environment, it does suggest that there is a base level of interference from the amygdala, and perhaps as soon as one area becomes more active or passes a certain threshold of activity, it is able to usurp the task from the other area, perhaps because it can handle that specific type of information more efficiently?

So far we have looked at the functional elements to memory consolidation and reconsolidation, but what is the role of the amygdala during the retrieval of memory? Fenka et al. (2005) arranged an fMRI based study where participants were asked to study a series of words that were exposed intermixed with both neutral faces and fearful faces; these words were later presented in a separate test where the participants had to respond that they remembered the word (conscious recollection of study), they knew the word (familiarity without conscious recollection), or that the word was simply new. The team found that there

was increased bilateral activation of the amygdala when participants remembered words from the study, rather than knowing them without conscious recollection; this could indicate the amygdala is pivotal for remembering something in a particular context, and perhaps the context facilitated the retention? The right amygdala became during the study of words that had been paired to fearful faces, as did the fusiform gyri; the fusiform gyri showed more activation for words paired with fearful faces than for neutral faces. However, during recollection the amygdala demonstrated no preference when recalling words in the neutral or fearful context. During retrieval, the amygdala appears to have lost its "fear" role and could simply be working with the fusiform gyrus and the hippocampus to retrieve memories.

The participants in the Fenka study, however, were not asked whether or not remembering the words was accompanied by a positive or a negative feeling, or anything that might hint at the fact that they had learned an obvious emotional association with the words. This matches the results from the Rubin study, where it was reported that even though there was increased amygdala activation during a particular moment of insight that would be remembered one week later, the participants reported no strong emotional feelings throughout the duration of the test. The moment of insight in the Rubin study was a moment where the participant suddenly became familiar with a previously camouflaged image, which makes one wonder if camouflaged images of pictures that the participant was intimately familiar with, i.e. knew the context surrounding the picture, if there would have be even more amygdala activation during the moment of insight.

We seem to be presented with a two-lane highway for information processing, and the amygdala becomes active and varies in function at different moments on this highway. The lateral amygdala seems to be the location for the synaptic coupling of the conditioned stimulus with the unconditioned stimulus, and is the site for increased transcription during the fragile moments of consolidation and reconsolidation. This activity seems to aid retention, but then during recollection, the activity must be aiding other limbic structures, i.e. the fusiform gyrus, to recall information, which could be conscious or unconscious recollection. A future study could perhaps determine levels of prefrontal cortex activation at the same time the amygdala is aiding the retrieval of memory.

Is the difference between short term and long term memory simply the difference between consolidation and reconsolidation? This would mean that anything that the amygdala helps to consolidate has a good chance of becoming long term memory, because as Parsons et al. (2006) found out the mRNA used for consolidation can be used again for reconsolidation, without needing to take the time for more transcription.

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