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The brain decade in debate: III. Neurobiology of emotion

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Abstract

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This article is a transcription of an electronic symposium in which active researchers were invited by the Brazilian Society of Neuroscience and Behavior (SBNeC) to discuss the advances of the last decade in the neurobiology of emotion. Four basic questions were debated: 1) What are the most critical issues/questions in the neurobiology of emotion? 2) What do we know for certain about brain processes involved in emotion and what is controversial? 3) What kinds of research are needed to resolve these controversial issues? 4) What is the relationship between learning, memory and emotion? The focus was on the existence of different neural systems for different emotions and the nature of the neural coding for the emotional states. Is emotion the result of the interaction of different brain regions such as the amygdala, the nucleus accumbens, or the periaqueductal gray matter or is it an emergent property of the whole brain neural network? The relationship between unlearned and learned emotions was also discussed. Are the circuits of the former the underpinnings of the latter? It was pointed out that much of what we know about emotions refers to aversively motivated behaviors, like fear and anxiety. Appetitive emotions should attract much interest in the future. The learning and memory relationship with emotions was also discussed in terms of conditioned and unconditioned stimuli, innate and learned fear, contextual cues inducing emotional states, implicit memory and the property of using this term for animal memories. In a general way it could be said that learning modifies the neural circuits through which emotional responses are expressed.

Key words

- Emotion
- Fear
- Anxiety
- Learning
- Memory
- Amygdala
- Nucleus accumbens
- Periaqueductal gray matter

Introduction

Emotion has long been recognized as an important drive for behaviors important to the survival of animal species. In humans it contributes to welfare and suffering, with an important role in psychiatric diseases. The efforts of psychologists and neuroscientists to create a scientific theory of emotion can be viewed in the theories and studies of Charles Darwin, William James, Sigmund Freud, James Papez, and Paul McLean, among others. The advances introduced by these scientists were followed by a long period of time in the middle of the 20th century during which both neuroscience and cognitive science neglected the emotional nature of the mind. Hopefully, in the so-called “Decade of the Brain”, a step forward was made by the attempts to join the progress of the cognitive neuroscience approach and emotion in a unified theory of mind (see, for example, the books of Damasio (1) and LeDoux (2)). Antonio Damasio (3) called this movement “a second chance for emotion”, in spite of the fact that today there are more disagreements than fully accepted theories for emotions (4). Nevertheless, some consensus has been reached in particular issues, like the role attributed to the amygdala in emotion. In order to discuss the scientific advances and views achieved in this field over the last decade, the Brazilian Society of Neuroscience and Behavior (SBNeC) organized a virtual symposium held on April 24, 2000. The chat site was provided by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq). The present article is based on the transcription of this symposium.

What are the most critical questions in the neurobiology of emotion?

Luiz Carlos Schenberg: From my point of view there are two sets of problems that should be worked out in the next years. The

first set is conceptual: Few areas of science have a conceptual framework as loose and imprecise and so influenced by common sense as the field of emotion. What are emotions? What are the differences between emotion, mood, drive, temperament and personality? Are drives and emotions distinct entities? How many emotions do we have? What are the differences between sadness, anxiety, fear, panic, happiness, love, sexual arousal, hunger, pleasure, aversion, etc.? Are there basic emotions? Is pain a sensation or an emotion? What is suffering? What do we mean by stress? How do these entities relate to each other? The second set of problems is experimental and deals with the specific contribution of any neural system to the genesis of emotions. Conversely, it also addresses the question if one neural system can express two or more kinds of emotions depending on its mode of operation. For instance, are anxiety and panic generated by different systems or by the different functioning of a single neural system? Hopefully, the solution of the second set of problems will help us answer the above theoretical questions.

Jean-Marc Fellous: Is there one emotional system, or are there several emotional systems? Is there an animal model of emotion (or of a particular emotion)?

Claudio Da Cunha: In my opinion the most critical questions in the neurobiology of emotion are: 1) What is emotion in a neurobiological perspective? 2) Which are the basic neurobiological systems involved in specific kinds of emotion? Which brain structures participate in the expression of different types of emotion and how do they do so? Is an emotion encoded in a specific brain region or is it a property of the interaction of the whole brain neural network? What is the participation of the different emotional brain systems in psychiatric diseases?

Joseph LeDoux: I will start with two obvious questions. First, are there different neural systems for different emotions? Second, how do we get from our understanding

of emotional reactions in the brain to emotional feelings?

Francisco Guimarães: What is the interaction between emotion and memory? How do emotional experiences induce lasting behavioral changes? What is the role of the hippocampal formation in emotion? What about the neurobiology of other emotional states (since a large part of the research has been done with a specific emotional state: fear)? And what is the neurochemistry of emotion, particularly the role of neuropeptides found in huge concentration in areas related to emotion?

Robert & Caroline Blanchard: We're at home with only one computer so our names will appear together. One critical issue is - What are the emotions? Taking the example of fear, we don't know if this involves one or several systems and if the latter how to differentiate and classify them. It probably will be possible to create a unified view of emotions, their evolutionary functioning and all, but to obtain a solid result this is going to have to rest on adequate analyses for at least some focal systems.

Jeffrey Rosen: Are there common neuroanatomical substrates for different emotions or are there separate systems? For example, the amygdala is important for fear conditioning, but evidence suggests it is also involved in appetitive conditioning. Are these overlapping systems using the same circuits or separate parallel circuits?

Joseph LeDoux: We all seem to be on the same track. The question then is what is the best way to figure this out. We have decent models of emotional behavior for studying fear, but less good models for other emotions. Appetitive conditioning, for example, doesn't have the same face validity for human emotion the way fear conditioning does.

Robert & Caroline Blanchard: We can muster a case for good models of aggression, as well as fear, the latter possibly involving more than one system anyway. Certainly

there is growing evidence for differential involvement of different aspects of (systems within) fear/defense in different psychiatric conditions.

James McGaugh: I think that we need to express some caution about concluding that we have good models for studying any emotion in animals. We have to consider both the autonomic expression and other aspects of expression of emotions.

William Irwin: In part related to Joseph's comment, at least at the human level, it is important to distinguish between the processes underlying the perception of emotionally salient stimuli from the neural substrates that "generate" emotion.

Luiz Carlos Schenberg: Jeffrey - At least in the periaqueductal gray matter there seems to be a great overlapping of systems, if not in the periaqueductal gray matter itself, systems elsewhere in the brain that are triggered by activation of a single site within the periaqueductal gray (5,6).

Jeffrey Rosen: Yes, the periaqueductal gray matter seems to be divided at least into active (escape) and passive (freezing, immobility) behavioral coordinating areas; however, these may be activated by different forebrain neural systems, one with projections from the hypothalamus and the other from the amygdala, respectively.

William Irwin: In part the route for preserved responses will be sense modality specific.

Luiz Carlos Schenberg: William, I agree with you but I would add to your comment that we should also differentiate processes that generate emotions from those which are merely executive of hard-wired behaviors (releasing mechanisms).

James McGaugh: I agree with Irwin's comment.

William Irwin: Getting back to the issue of different neural systems for different emotions, if you take the perceptual processes (in humans) with regard to facial expressions, then the amygdala appears not to be in-

involved with certain emotional states (e.g., anger).

James McGaugh: I think it is important to distinguish between the learning of an emotion (emotional response) and the influence of emotion on learning and memory. This is a critical distinction. I think it highly unlikely that an emotion is encoded in any specific brain region. Interactions among brain regions seem to be required.

Claudio Da Cunha: I agree with you, but sometimes it is not what it seems to people that are not working in this area but who are interested in reading the papers.

William Irwin: Indeed, McGaugh's distinction is important. Relatedly, Davis' group (7) have reported that there are different neural systems (e.g., amygdala) that are responsible for conditioned vs unconditioned fear responses.

Claudio Da Cunha: Dr. LeDoux, do you agree with Dr. McGaugh's opinion?

Joseph LeDoux: Yes, I do agree with Jim McGaugh about the difference between brain mechanisms of emotion and emotional influences on memory mechanisms.

James McGaugh: I agree with Irwin that it is important to distinguish between learned and unlearned emotional responses.

What do we know for certain about brain processes involved in emotion and what is controversial?

Jean-Marc Fellous: One possible approach is to focus on a particular emotion and study it exhaustively (from neurochemistry to behavior). This is the most conservative/traditional way and it brought about already plenty of information (fear conditioning, for example). But I am wondering if such an approach will not bias *a priori* the scope of research... What if there were no emotional centers/circuits *per se*, but rather emotion is an emergent property of existing computations...

Claudio Da Cunha: With respect to Jean-

Marc's comment, in our last chat (on neurobiology of learning and memory, see Ref. 8), Joaquin Fuster said that he believes we are living times of "a new phrenology more or less legitimized by the scientific method". Is this the case for the neurobiology of emotion?

Jeffrey Rosen: In reply to Jean-Marc's earlier comment, I agree that the brain probably did not develop as emotion systems *per se*, but as systems for rapid appraisal (neural computation) of incoming stimuli and generation of appropriate responses. Emotion may be an emergent property of this neural activity. For learning or rapid evaluation of already learned fear, the amygdala is performing many of these computations. For unlearned or innate fear I think it is not clear what the role of the amygdala is. Much of the appraisal of unconditioned emotional stimuli may be taking place in the sensory organs, thalamus or cortex.

Joseph LeDoux: Jean-Marc, it could easily be the case for emotion if you only look at human work, imaging, and lesions. I think it may be less of a criticism of the animal work that looks at mechanisms within and between cells as opposed to brain areas.

James McGaugh: I think we need to consider much more seriously the interconnectedness of brain systems mediating emotional responses and emotional influences. Several recent papers have reported that fear can be and is expressed in rats lacking an amygdala. Also, Joseph, you have shown that different aspects of fear are mediated by different amygdala nuclei (9).

Joseph LeDoux: Jim is right on target. We are very good at focusing on small pieces of the puzzle in neuroscience (on memory or perception or emotion or attention) and have done less well in understanding how all of these things come together to make us who we are.

Jean-Marc Fellous: It seems to me that in addition to asking 'what are the neurons/centers involved in emotion?', we should also ask 'how a particular set of neurons

computes during an apparent emotional state' (i.e., fast, slow, using synaptic changes, recruiting more/less cells...).

James McGaugh: Another important controversy is that of whether the same processes underlay learned and unlearned emotional responses. What do we know about that?

Joseph LeDoux: Almost everything is controversial. Regarding learned vs unlearned mechanisms, my own view is that learning modifies the circuits through which unlearned responses are expressed.

William Irwin: Regarding LeDoux's last statement about learning modifying a circuit, can you say a bit more about the nature of that modification? Is it more like a parameter adjustment? Do certain structures go "off line" and do certain structures go "on line" (i.e., a transfer of function)?

Joseph LeDoux: I had in mind the switching of inputs. Natural stimuli turn the system on and through learning novel stimuli gain access. I base this in part on Blanchard's early work with rat fear of cats (10). But Jeff Rosen's new data question this to some extent. We need more work on what "unconditioned" fear is.

Eliane Volchan: If an unlearned visual fear response like that for looming does not involve the amygdala, it is difficult to imagine the switching of inputs needed for conditioning to novel stimuli. Shouldn't the same basic circuit be involved in order to be modified by the learning experience?

James McGaugh: I heartily agree that we need to know more about the nature of unlearned emotions (including but not restricted to fear).

Robert & Caroline Blanchard: While the learned-unlearned fear distinction is important (go to it, guys), we sense a disturbing lack of attention to the specifics of the neurobehavioral systems that regulate defense *per se* (never mind emotion, until you get the basics down). These are beautifully complex sensorimotor systems and should provide

the basis for analyses of the neurobehavioral systems controlling at least one type of emotion.

Jeffrey Rosen: In regard to learned and unlearned emotional responses, I think the circuits may be different. We have lesion data showing that the lateral, basolateral and central nuclei of the amygdala are important for conditioned fear (freezing), but not for freezing to a predator odor. We're not yet sure what the systems are for freezing to predator odor.

Luiz Carlos Schenberg: Jeffrey, may be there is an involvement of the medial amygdala. Unpublished data from our laboratory suggest an important role of the medial amygdala in fear-like behaviors (immobility, trotting). The Blanchards have convincing data as well (11,12).

Eliane Volchan: Joseph, going back to the issue of learning modifying unlearned circuits: How does a learning fear experience (which involves the amygdala) modify a circuit of unlearned fear, if the amygdala was not involved in the first place?

Joseph LeDoux: The way I see it is that the emotional responses elicited by dangerous stimuli are hard-wired outputs of the amygdala. These outputs are engaged when the amygdala is turned on. Some things that turn on the amygdala do so because of evolutionary wiring. Others do so because of learning. The natural or unlearned or evolutionary stimuli are prewired to access the hard-wired response circuits. Other things can enter those circuits if they activate the circuits at the same time that a natural stimulus does. Electric shock, being a form of pain elicited by tissue damage, naturally activates the amygdala. Amygdala cells are responsive to shocks and also to tones. And if the shock comes on while the tone is activating the amygdala, the tone acquires the ability to activate the amygdala as well. This is a standard Hebbian interpretation of plasticity.

Eliane Volchan: Joseph, in that case, the same basic circuit should be involved to be

modified by the learning experience. What happens if the amygdala is not involved in the first place?

Joseph LeDoux: I think I sort of answered this above. But basically, for any part of the brain to learn an association between two stimuli, those two stimuli have to have some impact on that part of the brain. In this sense the amygdala has to be involved in the first place (which I assume means it responds to the unconditioned stimulus) if it is to be involved in the second place (if it is to learn).

Claudio Da Cunha: Talking about controversy - why do medial amygdala nuclei participate in fear behavior but not modulate memory? Are these two processes correlated or not?

Joseph LeDoux: I am not sure of the role of the medial amygdala in fear. Damage has no effect on fear conditioning, at least when we have done it, but the medial amygdala is connected with the paraventricular nucleus and may be involved in stress hormone release.

Luiz Carlos Schenberg: Stimulation of the medial amygdala elicits responses resembling those of the periaqueductal gray such as immobility and trotting and Blanchard and colleagues (11) showed taming of wild rats by lesioning the medial amygdala.

James McGaugh: Have brain imaging studies revealed anything critical about differential brain systems involved in different types of emotion?

Claudio Da Cunha: From what I have read, I agree with the opinion of Dr. Baddeley in the other chat (8): at present brain imaging has just proved what we already knew about these processes. Now it is time to use it to answer new questions.

Joseph LeDoux: Jim, there are some imaging studies that show different activations to different emotional stimuli (faces) (13). I am not sure if this really addresses your question but I think that may be all that exists.

William Irwin: Could McGaugh comment further on this point: We know that “emotion enhances memory” but does the magnitude of the emotion correlate with the degree of memory enhancement?

James McGaugh: The strength of memory varies with the intensity of stimulation used to induce the memory and with the degree of release of catecholamines - particularly norepinephrine in the amygdala.

Francisco Guimarães: Related to William’s question another issue is: Could a negative emotional experience introduce a bias in memory (for example, facilitating memories of other negative events)? There are some studies with depressive patients suggesting this.

William Irwin: At the human level, it is important for us to systematically examine the relation between “self-reported” emotion (that is, at a neural level it is important what people say/feel about their emotional states) and brain systems. We are examining this with neuroimaging techniques. Also, note the obvious statement that this can’t be done in non-human animals.

Joseph LeDoux: It is true you can’t use “self-reporting” in animals but it’s important to also remember that just because you can use “self-report” in humans doesn’t mean that’s the key to emotions or other aspects of mental life (other than the aspects that are accessible to self-report). I am sure that’s what you meant but I just wanted to make it clear.

William Irwin: Yes, thank you for that clarification. To further add (and related to your comments about learning modifying a neural circuit), the (human) process of feelings may be an important component that modifies the underlying neural substrata (of course, an obvious territory would be the prefrontal cortex).

James McGaugh: But, we can do a reasonably good job of getting at something like “self-reporting” in animals by asking them a lot of questions that they can answer behav-

iorally (i.e., by testing them in various ways). There are a lot of ways, for example to find out what animals like and whether they know how to find what they like and remember where it is. This is a bit like self-reporting but probably more believable!

What kinds of research are needed to resolve these controversial issues?

Claudio Da Cunha: It would be a good idea if each of us stated in a few words what we are doing in our laboratories to address these controversial issues on neurobiology of emotion.

James McGaugh: We find that lesions of the basolateral amygdala block the memory-modulating (enhancing or impairing) effects of post-training drug and hormone infusions into other brain regions - including, but not restricted to, the dorsal hippocampus. The same effects are found with beta-adrenergic antagonists infused selectively into the basolateral amygdala (14). Similar effects have been reported by several other laboratories studying basolateral amygdala influences on dentate gyrus long-term potentiation. Basolateral amygdala lesions block the long-term potentiation and basolateral amygdala stimulation enhances it (15,16).

Jeffrey Rosen: In our laboratory we are studying immediate early gene expression in the lateral nucleus of the amygdala with fear conditioning. Early growth response gene 1 (EGR-1; also called zif268) mRNA increases with conditioning, but not during retrieval (17). Does that mean the amygdala plays different roles in acquisition and retrieval of fear?

Claudio Da Cunha: In my laboratory we did some experiments showing that “anxious” and “non-anxious” rats present correlated behavior in learning and memory tasks (18). I suppose this is in agreement with Jean-Marc’s view of an interconnected network. More recently I started to study rats

with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) lesions in the substantia nigra pars compacta. It seems to me that some “emotional” aspect may also be encompassed by the prefrontal cortex/striate circuitry (unpublished data).

Francisco Guimarães: We found that poststress facilitation of 5-HT_{1A} (19) or blockade of NMDA-mediated neurotransmission in the dorsal hippocampus inhibits the decrease in open arm exploration found 24 h after a 2-h period of restraint stress.

Luiz Carlos Schenberg: I do believe that anxiety and panic are triggered by phenomena within the amygdala and periaqueductal gray, respectively. Similar to the blunted neuroendocrine response of panic attacks in humans (20,21), our recent results showed that neither plasma ACTH nor prolactin levels change following a 1-min full-blown defense reaction induced by stimulation of the dorsal periaqueductal gray matter. Moreover, the dorsal periaqueductal gray matter-induced defense reaction was attenuated by 21-day administration of clomipramine (22).

Francisco Guimarães: An interesting finding with clomipramine. What do you think about the initial worsening that this drug might cause in panic patients?

Luiz Carlos Schenberg: There was no “worsening”, i.e., threshold reduction, in intermediate sessions. In turn, fluoxetine (1 mg kg⁻¹ day⁻¹) which is a less efficient panicolytic but a selective 5-HT reuptake inhibitor, attenuated galloping only.

Robert & Caroline Blanchard: Was that acute fluoxetine? In our laboratory acute and chronic fluoxetine have opposite and strong effects on flight, so your “galloping” is very interesting.

Luiz Carlos Schenberg: Chronic fluoxetine test trials were performed before the daily dose so as to avoid the acute effect. Robert, it is interesting that neither acute diazepam and buspirone nor a 10-day treatment with buspirone caused any threshold

increase in periaqueductal gray matter-induced defensive responses.

Robert & Caroline Blanchard: Which periaqueductal gray matter-induced defensive responses?

Luiz Carlos Schenberg: Immobility, trotting, galloping, micturition, defecation, jumping, and exophthalmus.

Robert & Caroline Blanchard: Related to panic, we have been examining results from a wide array of panic “models” and one possible interpretation of these is that anti-panic and panicolytic drugs work very selectively on flight, but that when flight is elicited lower and lower in the system (i.e., experimentally *vs* stimulation of dorsomedial hypothalamus *vs* periaqueductal gray matter) some variability creeps into the system, suggesting that these drugs may act along the route, having less effect near the end (23).

William Irwin: I think there are different (likely overlapping) neural substrata that govern “preferences” (as you describe) versus “feelings” (self-reported). Note that if we are going to be honest with ourselves, a truly comprehensive neural theory of emotion is necessarily going to have to deal with “feelings” (whatever they may be).

James McGaugh: Much of the focus of emotional research has, of course, been on aversively induced emotional states. How are we to study positive emotional states? Any guess about the brain processes involved?

Claudio Da Cunha: Talking about positive reinforcers, could the nucleus accumbens play a more important role than the amygdala in this case?

James McGaugh: The nucleus accumbens is certainly involved. Nucleus accumbens lesions produce effects like those of stria terminalis and basolateral amygdala lesions in blocking the effects of stress hormones on memory - even if the stress hormone agonists are infused into the dorsal hippocampus.

Jean-Marc Fellous: Claudio - It does go in the direction of emotion as an interacting circuit. But I would like to push further... The fact that two regions are communicating during an emotional state is interesting and important to know. What I was trying to say is that very little research is done on parametrizing the communication (is it fast, slow, how many neurons are involved, what is the timing of spikes, what neuromodulators are involved?) Perhaps this level of description could be useful to characterize/understand the emotional state... For example, the amygdala is involved in fear conditioning to tone and the hippocampus is involved in conditioning to context: Are stimuli routed with respect to their complexity? Can this be changed/modulated in cases where ‘fear’ is not involved? This surely would help a computational neurobiologist like me...!

James McGaugh: Although we know that the amygdala is involved in fear conditioning the meaning of “involved” needs serious consideration. Our findings (24,25) and those of many other recent studies (26,27) clearly indicate that the amygdala has a modulatory role in influencing storage in other brain systems. We find no evidence that the amygdala is a site of storage for any kind of fear conditioning (28).

Jean-Marc Fellous: I do think that modulation of activity, rather than activity itself, is where a lot can be learned about emotion... Very much in your line of thought...

Jeffrey Rosen: For positive emotions, I think the nucleus accumbens is probably involved. Interestingly, LeDoux and others (9) are finding that learning of active avoidance behavior seems to involve the basal nucleus of the amygdala, but not the central nucleus. Because the basal nucleus projects to the nucleus accumbens, it is possible that the nucleus accumbens plays a role in active avoidance. Since avoidance is a coping response to an aversive event there are probably positive emotions associated with it. If the nucleus accumbens is part of an avoid-

ance circuit, positive emotions should emerge during avoidance.

Claudio Da Cunha: Related to Dr. McGaugh's proposition, a long time ago I read some papers suggesting that the amygdala and some processes may be equally involved in both positive (reward) and aversive behaviors (29).

Joseph LeDoux: The work of Everitt and Robbins (30) has helped clarify the role of the amygdala and nucleus accumbens. The amygdala seems important for learning about incentives and the nucleus accumbens is where dopamine amplifies the incentive value of the stimulus coming from the amygdala, if I have got their ideas right.

William Irwin: With regard to the amygdala/accumbens interactions, I believe it is the case that while there are no amygdalofugal projections to the ventral striatum, there are projections in the reverse. It's not clear exactly how to interpret these findings, but I think they are important to consider.

Claudio Da Cunha: Other evidence for the participation of the amygdala in both aversive and reward tasks is that the actions of benzodiazepines are mediated by the basolateral amygdala and they block the extinction of an aversive conditioning caused by the learning of a secondary task (31). What do you think about it?

James McGaugh: As benzodiazepines induced amnesia in humans (32) - for all kinds of learning - it seems reasonable to conclude that they affect positive as well as negative learning.

Jeffrey Rosen: Do benzodiazepines change thresholds in the amygdala?

Luiz Carlos Schenberg: I did not test it on thresholds, but it was shown long ago that microinjection releases punished behavior (33).

James McGaugh: Benzodiazepines do not affect memory in animals with basolateral amygdala lesions (34). Thus, the benzodiazepine receptors in the amygdala are critical for memory effects.

Luiz Carlos Schenberg: Interestingly, stimulation of the central nucleus of the amygdala produces only immobility (unpublished data).

Claudio Da Cunha: Does this immobility mean an emotional state? Is it related to the memory processes modulated by the basolateral nucleus of the amygdala?

Luiz Carlos Schenberg: I do not know if this is tense immobility such as in freezing, not quiescent immobility.

Jeffrey Rosen: So how do you see the role of the amygdala and periaqueductal gray matter in fear (anxiety) vs panic?

Luiz Carlos Schenberg: Flight is the typical response of periaqueductal gray matter, not of the amygdala, and is the response most sensitive to panicolytics (22).

What is the relationship between learning, memory and emotion?

Robert & Caroline Blanchard: Related to learning, we think some attention to an additional distinction might be profitable. Typical paradigms explore the relationship between pain and contextual or point stimuli. What about nonpain stimuli such as predators as the unconditioned stimulus in context or other types of learning? Predator-context associations constitute a significant paradigm in the real world and have the advantage of enabling us to systematically add pain activation to analyses.

Jeffrey Rosen: Predator odor does not seem to act as a good unconditioned stimulus. We don't get context conditioning to a predator odor, although the predator odor elicits robust freezing (35).

James McGaugh: Have you tried many kinds of odors and intense odors?

Jeffrey Rosen: Jim, fox odor (trimethylthiazoline) elicits robust freezing for long periods of time (at least 15 min). We also get a very nice dose-response curve with small amounts of fox odor. We have tried to elicit freezing with butyric acid, caproic acid and

isoamyl acetate at amounts 100 times more than the fox odor. Only isoamyl acetate gives us moderate levels of freezing when used in very large amounts (35). We have tested two other animal odors (besides caproic acid). Fox urine elicited freezing, while mouse urine did not.

Luiz Carlos Schenberg: Odors are implicit memory, we can recognize them but not recall, may be this is the point.

Joseph LeDoux: Most things that humans are emotional about are things we have learned about in one way or another. Memory is therefore very important in emotion. Both explicit and implicit memory, and vice-versa. Emotions, once aroused, strongly influence memory, but Jim should talk about that.

James McGaugh: We can certainly learn to be emotional in the presence of cues that previously induced the emotion. We all agree on that. But emotion can also, as discussed above, modulate the degree of memory of the specific events (i.e., declarative memory) that elicited the emotional arousal. And, we know that this involves the release of stress hormones, the activation of the basolateral amygdala (release of norepinephrine) and activation of other brain regions including the insular cortex and hippocampus.

William Irwin: Are the emotion-enhancing effects on explicit/declarative types of memory the same for implicit types of memory?

James McGaugh: Does anyone know how to study implicit memory in animals? We would need to know that in order to answer Irwin's question.

Joseph LeDoux: Jim, did you mean implicit or explicit memory in your question about animals?

James McGaugh: I meant "implicit" but I said that because it is not clear to me how we can clearly distinguish between implicit

and explicit memory in animals - can we specify those prior to conducting any particular experiment? In the case of human subjects the distinction is clear on the basis of priming experiments. But do we have the same clear evidence for animal studies?

Joseph LeDoux: I tend to think of most memory in animals and humans as implicit. In humans we have some sense that explicit memory is what happens when information that was encoded by the hippocampus is retrieved and placed in working memory. At most, then, we should think of explicit memory in animals as this kind of hippocampal based memory. But it is also possible that other animals have little or no explicit memory (at least the kind of explicit memory that we talk about in humans). So for me most memory in animals is implicit. This terminology is sort of backwards since implicit can only be defined by contrast to explicit, and it is likely that explicit came later in evolution.

Eliane Volchan: Does anyone know the role of the superior colliculus in the circuit of positive and negative emotions? For the visual system it is known that the superior colliculus feeds the pulvinar on the way to the amygdala.

Luiz Carlos Schenberg: Michael Davis (36) showed that the superior colliculus is involved in fear potentiation of acoustic startle by visual cues.

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