national centre for biological sciences
tata institute of fundamental research

Subject: Letter of recommendation for **Mr. Animikh Roy**

October 17, 2015

To whom it may concern:

It is a pleasure to express my strongest support for Animikh Roy's application. Animikh has been doing an internship under my supervision, from 22nd June, 2015, at the National Center for Biological Sciences (NCBS), Bangalore.

His work, which is currently in progress, involves an experimental study and mathematical modelling on lab rats. It focuses on finding specific patterns in the qualitative regions of the brain which deal with emotional responses such as the amygdala and its impact on social behaviour. He is specifically researching to determine whether neuronal responses in the lateral amygdala follow logarithmic patterns with respect to fear stimulus and he is also modelling a mathematical connection in terms of social behaviour.

He aims to achieve this through graphical representations with respect to changes in entropy of rats while under stress or exposed to a social aversive call at 22 KHz. He is also mapping a statistical distribution with respect to position and time to determine the net displacement vector which would help determine the directional preference of these rats in response to such aversive calls. He will then repeat the same process of data analysis on rats with portions of their amygdala surgically removed and observe the expected changes in patterns of behaviour.

He plans to compile all his data and present a comprehensive inference which he hopes to publish in the near future. Based on my interactions with Animikh and his work in my lab, I am convinced that he belongs to that select group of gifted and thoughtful students who have the creativity, focus, temperament, and rigor to flourish in academics and research. I sincerely hope that you will consider Animikh's application favorably.

Sincerely,

S. Chattarji

Professor Sumantra Chattarji
National Centre for Biological Sciences (NCBS)
Tata Institute of Fundamental Research

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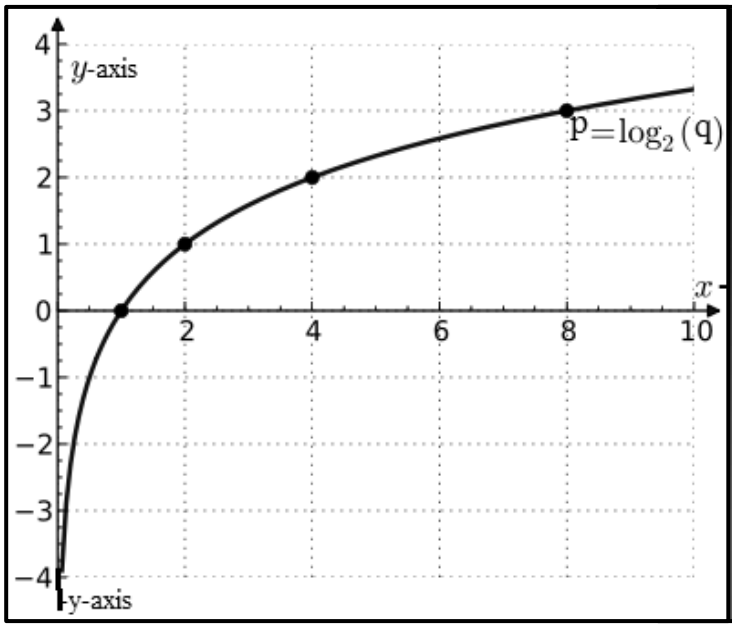
Quantifying Emotions: Analysing Logarithmic Responses in the Lateral Amygdala forNeuronal Correlates of Fear & Pain:



By

Animikh Roy

ABSTRACT

Understanding the brain and decoding its mysteries undoubtedly tops the list of the frontier challenges that Science encounters in the 21st Century. Recent discoveries in Neuroscience have enabled us to look at some of these mysteries with unprecedented depth and clarity using the crafts of modern technology. One such advancement sheds new light on the processing and representation of fear with respect to neuronal activity in the Amygdala, while the other enables us to comprehend the neuronal implementation of number representation in the brain. In other words, recent works by Nieder and Miller demonstrate a neural correlate of the Weber-Fechner's law which talks about a Logarithmic mental number-line. In this article, we shall explore both these aspects of neuronal correlates of fear as experimentally recorded in the Amygdala along with the general mathematical representation of the number-line in the brain which happens to follow the logarithmic scale. We will then discuss some recent experiments which show a strong connection between these apparently disconnected activities of the brain and demand a new synthesis of understanding of fear and pain as the brain represents them. In doing so, we attempt to discuss a new quantitative approach to understanding qualitative or emotional activity in the brain by investigating a numeric or rather logarithmic representation of the experience of fear and pain in the amygdala. This research may provide vital insight with respect to the study and cure of Post-Traumatic-Stress-Disorders, Post-Traumatic-Visual-Disorders and other disorders related to fear and trauma.

Introduction

"The human brain, it has been said, is the most complexly organised structure in the Universe"

-V.S. Ramachandran

Till the latter half of the 20th Century, it was fashionable for many scientists to separate psychology from the study of the brain. This, separatist point of view created a prominent obstacle in reaching a comprehensive conclusion while examining the numerous enigmas of the brain. Functionalist philosophers such as Jerry Fodor convinced a generation of psychologists that the comprehension of the mind demanded the development of purely computational theories, without any need for biological implementation. The computer metaphor promoted a logical separation of the software from the hardware, and lead inevitably to the conclusion that the details of the neural machinery were irrelevant to the psychological enterprise.

Today, however, we know that this view was unnecessarily narrow. The new methodologies in cognitive neuroscience allow for an interdisciplinary approach which is far more rigorous and full-proof. Neuroscientists of the 21st Century, routinely mix psychological and neural observations in the same experiments. Psychological concepts have become an integral part of Cognitive Neuroscience and are not ruthlessly eliminated, as was initially foreseen by most philosophers. Rather, they are enriched, constrained and transformed by the analysis of neural data. For example, the learning and remembering of fearful events was always thought of as dependent on the integrity of the Amygdala.

However, we were technologically limited in the 20th Century to understand how exactly fear and pain are represented in the activity of the Amygdala neurons? On the other hand, today we are testing these very tenets of philosophy and psychology with actual verifiable experiments which provide deepest insight into the subject. Here, we shall review recent electrophysiological studies indicating that neurons in the lateral amygdala encode aversive memories during the acquisition and extinction of Pavlovian fear conditioning. These studies have combined unit recording with brain lesions and pharmacological inactivation to provide evidence that the lateral amygdala is a crucial for representing pain and fear. Extinction of fear memory reduces associative plasticity in the lateral amygdala and involves the hippocampus and prefrontal cortex. Understanding the signalling of aversive memory by amygdala neurons opens new avenues for research into the neural systems that support fear behaviour

On the other hand, in a recent article, Andreas Nieder and Earl Miller provide a beautiful illustration of the mental number-line by showing how the study of the neural coding of number can resolve a classical problem in psychophysics which questions: what is the mental scale for numbers? In the latter half of the 19th century Weber and Fechner had proposed a probable insight into the mental scale problem in which they suggested that the resolution of human perception diminishes for stimuli of greater magnitude. Weber and Fechner had devised certain rudimentary schemes and experiments which seemed clearly indicate saturation in perceived stimuli with repeated linear increase of external stimulus. However, this evidence was not

convincing enough for the scientific fraternity, and it is only in the light of recent Cognitive-Neuroscience experiments that scientists can conclude with fair amount of certainty regarding number scale and representation in the brain.

In the coming sections we will highlight and some important experimental research in Neuroscience which clearly supports the fact that the brain follows the logarithmic number scale for certain evolutionary advantages and efficient decision making. We will then discuss another branch of experimental Neuroscience which deals with the direct recording of neuronal activity related to pain and fear memory. In the very last section we will conclude by discussing on-going experiments which propose the merger of the logarithmic brain-scale and the direct neuronal recordings with respect to pain and fear to figure out if the brain represents these emotions on a similar scale. The implications of such findings will be discussed along with interesting possibilities that may arise out of this work.

Mental scaling: Linear, Logarithmic, or Power Function?

The 'scaling problem' was integral to the birth of psychology as a scientific discipline. Founding fathers of experimental psychology, including Weber and Fechner considered as one of their central goals the mathematical description of how a continuum of sensation, such as loudness or duration, is represented in the mind. They identified the basic regularities of our psychological apparatus by careful psychophysical experiments, often requiring thousands of discrimination trials on pairs of stimuli. Ernst Weber discovered what we now know as Weber's Law: over a large dynamic range, and for many parameters, the threshold of discrimination between two stimuli increases linearly with stimulus intensity. Later, Gustav Fechner showed how Weber's law could be accounted for by postulating that the external stimulus is scaled into a logarithmic internal representation of sensation.

Weber found that the "Just Noticeable Difference" also called JND between two weights was approximately proportional to the weights. Thus, if the weight of 105 g can (only just) be distinguished from that of 100 g, the JND(or differential threshold) is 5 g, or in the SI system, a force or weight of 0.005 kg N. If the mass is doubled, the differential threshold also doubles to 10 g, so that 210 g can be distinguished from 200 g. In this example, any weight for that matter seems to have to increase by 5% for someone to be able to reliably detect the increase, and this minimum required fractional increase (of 5/100 of the original weight) is referred to as the "Weber fraction" for detecting changes in weight. Other discrimination tasks, such as detecting changes in brightness, or in tone height (pure tone frequency), or in the length of a line shown on a screen, may have different Weber fractions, but they all obey Weber's law in that observed values need to change by at least some small but constant proportion of the current value to ensure human observers will reliably be able to detect that change.

This kind of relationship can be well quantified by the following differential equation:

$$\boldsymbol{dp = K\left(\frac{dS}{S}\right)}$$

Where, $\boldsymbol{dp}$ is the differential change in perception $\boldsymbol{dS}$ is the differential increase in the stimulus, and S is the instantaneous stimulus. The parameter $\boldsymbol{K}$ is to be estimated using experimental data.

Integrating the above equation, we get:

$$\boldsymbol{p = Kln\, S + C}$$

Where, **C** is the constant of integration and $\boldsymbol{ln}$ is the natural logarithm.

To solve for $\boldsymbol{C}$, we simply put $\boldsymbol{p = 0}$, that is the condition for no perception. Then we subtract $\boldsymbol{Kln\, S_0}$ from both sides and rearrange to get:

$$\boldsymbol{C = -K\, lnS_0}$$

Where, $\boldsymbol{S_0}$ is that threshold of stimulus below which there is no perception of stimulus at all. Now, substituting this value in for C above and rearranging, our equation becomes:

$$\boldsymbol{p = k \ln\left(\frac{S}{S_0}\right)}$$

Therefore, mathematically we can establish a quantifiable relationship between stimulus and perception which is logarithmic in nature. This logarithmic relationship means that if a stimulus varies as a geometric progression (i.e. multiplied by a fixed factor), the corresponding perception is altered in an arithmetic progression (i.e. in additive constant amounts).

Let us now demonstrate this with the help of an example. Let us say that, a stimulus is tripled in strength (i.e. 3 x 1), the corresponding perception may be two times as strong as its original value (i.e., 1 + 1). Now, if this stimulus is again tripled in strength (i.e. 3 x 3 x 1), then the corresponding perception will be three times as strong as its original value (i.e. 1 + 1 + 1). Hence, for multiplications in stimulus strength, the strength of perception only adds. The mathematical derivations of the torques on a simple beam balance produce a description that is strictly compatible with Weber's law.

Fechner did not conduct any experiments on how perceived heaviness increased with the mass of the stimulus. Instead, he assumed that all JNDs are subjectively equal, and argued mathematically that this would produce a logarithmic relation between the stimulus intensity and the sensation. Other sense modalities provide mixed support for either Weber's law or Fechner's law. More recently, Stevens discussed the possibility that the internal scale is a power function rather than a logarithm, and Shepard introduced the multidimensional scaling method as a means of estimating, without a priori assumptions, the geometrical organization of an internal continuum.

Although Weber and Fechner concentrated on perceptual continua such as loudness, Stevens and Shepard showed that more abstract parameters, including our sense of number, also followed Weber's law. In spite of these brilliant analyses, often based on solid mathematical foundations, the Fechner–Weber– Stevens debate was never fully resolved. One of the reasons is that there are basic mathematical ambiguities in the modelling of behavioral data. Moreover, experiments could not be efficiently designed to record data directly with respect to neuronal activity and experiments were restricted to the study of behavioral data instead.

In particular, given suitable assumptions, both logarithmic and linear models of the internal scale are tenable. Fechner's logarithmic scale easily accounts for Weber's finding: if the scale has a fixed internal variability, then doubling the value of the compared quantities leads to a corresponding halving of discrimination power. However, the same discrimination function can also be accounted for by postulating a linear internal scale with a corresponding linear increase in the standard deviation of the internal noise. In the case of the mental representation of number, Gallistel has argued that the linear model should be preferred because it allows for a simpler calculation of sums and differences. Contrary to that, Changeux and Stanislas Dehaene have proposed a simple neural network of numerosity detection that assumes a logarithmic encoding of number, thus avoiding an explosion in the number of neurons needed as the range of internally represented numbers increases. This also supports the Bayesian model of the brain that enables it to take effective decisions in the quickest way operating on the log scale. Dehaene also argues, that the psychological predictions of the linear and logarithmic models are essentially equivalent with the possible exception of a novel psychophysical paradigm. It is hard to see how behavioural observations alone could ever disentangle the linear and logarithmic hypotheses. Therefore, modern neuroscience experiments focus on direct neuronal data from the brain via in-situ recording to arrive at a decisive conclusion. This will be demonstrated in the following portions.

The Neuronal Code for Number

The ability to record from neurons that are assumed to constitute the neural basis of the psychological number Corresponding scale now brings direct physiological evidence to bear on this issue. In the early days of neurophysiology, a few neurons that encoded number were reported in the association cortex of the cat, although this initial discovery was quickly forgotten.

In 2002, however, two papers, one recording in parietal cortex and the other in prefrontal cortex, reported the observation of neurons whose firing rate was tuned to specific numerosity. A given neuron, for instance, might respond optimally to three visual objects, a little less to displays of two or four objects, and not at all to displays of one or five objects. This offered a unique opportunity to examine the neural code for an abstract psychological continuum. As noted by Nieder and Miller, it is particularly interesting to investigate the neural basis of Weber's law with an abstract dimension such as number. For parameters that are more closely dependent on sensory physiology, such as loudness, weight or brightness, there is often evidence that the stimulus compression occurs at a peripheral sensory level. In the case of number, however, there are no obvious limitations in our ability to perceive multiple objects or sounds.

Furthermore, in human subjects, Weber's law is even observed with symbolic stimuli such as Arabic digits. Thus, it is likely that Weber's law for numbers is determined solely by the internal organization of cortical representations.

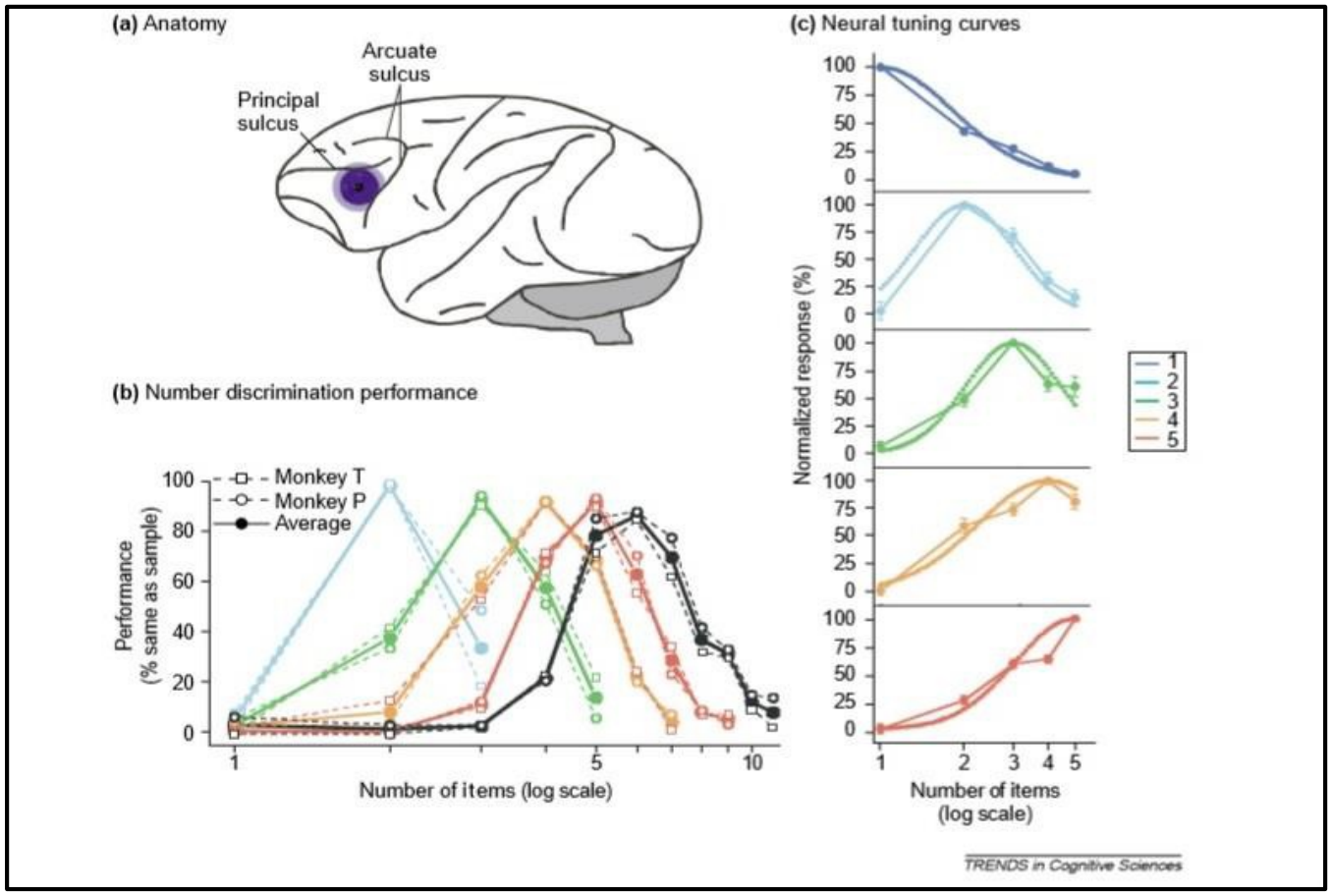


Figure (1): ***Evidence for logarithmic coding of number in the monkey brain. (a) The anatomical location in monkey prefrontal cortex where Nieder and Miller recorded number neurons. In their experiments, monkeys were presented with a first set of dots, which they were then asked to discriminate from a second set of dots. (b) The percentage of trials on which they responded 'same' is plotted as a function of the second number (abscissa) for different values of the first number, which ranged from 2–6 during behavioral testing (color of plot). Performance decreased smoothly with the distance between the two numbers (i.e. the peak occurs when the two numbers are the same). This distance effect assumed a Gaussian shape when plotted on a logarithmic scale. (c) So did the tuning curves of individual number neurons (shown for 1–5).***

In their paper, Nieder and Miller analysed in minute detail the behavioural and neural response curves of two monkeys, which had been engaged in a task of discriminating the numerosity of two visually presented sets as shown in Figure (1). They found clear evidence for Weber's law. Both animals showed a linear increase in their discrimination thresholds as the numerosity increased. Furthermore, the data were sufficiently regular to allow for a detailed analysis of the exact shape of the response distributions. When plotted on a linear scale, both behavioural and neural tuning curves were asymmetrical, and assumed a different width for each number.

Both sets of curves, however, became simpler when plotted on a logarithmic scale: they were fitted by a Gaussian with a fixed variance across the entire range of numbers tested (Fig.(1) b, c).Thus, the neural code for number can be described in a more parsimonious way by a logarithmic than by a linear scale. It should be stressed that this form of internal representation was not imposed by the training scheme the monkeys had. Training was based solely on the numbers 1 to 5, which were presented with roughly equal frequency. The optimal coding scheme would therefore have been a linear code with an exact encoding of each number 1, 2, 3, 4 and 5. The fact that the monkeys could not help but encode the numoricities on an approximate compressed scale confirms that this approximation mode is the natural way that number is encoded in a brain without language.

Future prospects the monkey data of Nieder and Miller are just a first stab at the problem from the neurophysiological standpoint, and do not fully resolve the Fechner–Weber–Stevens debate yet. When, Nieder and Miller fitted their data with a power function, they obtained a much worse fit than obtained with the logarithmic scale. According to them, to discriminate the power and the logarithmic functions in future experiments, it will be important to increase the range of numbers tested. We know from behavioural paradigms that, once trained with small numerosities, monkeys generalize to larger numbers up to 10 or more.

This is another proof that the numerical ability of animals is not merely inculcated in them by laboratory training, but is inherent in their mental toolkit. It is already remarkable that one can discriminate linear and logarithmic coding schemes with a range of numbers as small as1to5.By testing the neurons with a greater range of numbers; it should be easier to see if the small advantage of the logarithmic fit over the power function fit found over the range 1 to5 will continue to hold with larger numerosities. Overall, Nieder and Miller's recordings confirm Fechner's intuitions which were formulated over 130 years ago. The neural representation of number is comparable to the slide rule that some of us learned to use before the advent of electronic calculators, which was also graduated with a logarithmic scale. The advantages of this instrument are two-fold.

First, it was compact enough to allow the processing of arbitrarily large numbers with a pocket-sized device. Second, it ensured accuracy proportional to the size of the numbers involved something that was pertinent for real-life engineering applications. Perhaps the very same reasons can explain why nature selected an 'internal slide rule' as its most efficient way of doing mental arithmetic. Furthermore, according to Lav Varshney of MIT, the Bayesian model of the brain allows for the logarithmic scale because of evolutionary factors; so that the brain is hardwired in the most efficient manner with respect to probabilities and also in terms of signal transmission. This makes the brain Bayes-Optimal giving it maximum evolutionary advantage. Keeping this in mind, in the following section we shall discuss certain advanced techniques to measure pain and fear response in rats using modern tools of technology. This might serve as a vital basis for contemporary experiments on the logarithmic brain while taking into consideration its emotional representation in the Amygdala and the Thalamus.

Neuronal Correlates of Pain and Fear

If there is one central tenet of the neurobiology of learning and memory, it is that plasticity in the Central Nervous System (CNS) is essential for the representation of new information. Neuro-plasticity or brain plasticity refers to the brain's ability to *CHANGE* through•out life. The brain has the amazing ability to reorganize itself by forming new connections between brain cells or neurons. In addition to genetic fac•tors, the environment in which a person lives, as well as the actions of that person, plays a role in plasticity.

Neuro•plasticity occurs in the brain typically in the following way:

1) At the beginning of life: when the immature brain organizes itself.

2) In case of brain injury: to compensate for lost functions or maximize remaining functions.

3) Through adulthood: whenever something new is learned and memorized experience-dependent plasticity in the brain might take many forms, ranging from the synthesis and insertion of synaptic proteins to whole brain synchronization of neuronal activity.

An important challenge here is to understand how these various forms of experience-dependent plasticity are reflected in the activity of neuronal populations that support behaviour. Donald Hebb referred to these populations as cell assemblies, and this concept has had important heuristic value in empirical studies of the neurobiology of memory. With the advent of modern electro-physiological recording techniques, Hebb's concept of the cell assembly is now amenable to experimental study in awake, freely behaving animals. Using parallel recording techniques, multiple extracellular electrodes can be used to 'listen' to the action-potential dialogue between several neurons at once. In this article, we review recent single-unit recording studies that have provided considerable insight into the neuronal mechanisms of learning and memory, focusing particularly on Pavlovian fear conditioning. In this form of learning, a neutral stimulus such as an acoustic tone (the conditional stimulus, or CS) is paired with a noxious unconditional stimulus (US), such as a foot-shock. Furthermore, extracellular electrical signals in the amygdala with respect to the specific behaviour of freezing in synchronization can be recorded as a quantitative measure of pain experienced by the animal during the foot-shock stimulus.

It has been experimentally observed and recorded, that after only a few conditioning trials; the CS comes to evoke a learned fear response (conditional response, or CR). Pavlovian fear conditioning is particularly suitable to electrophysiological analysis because it is acquired rapidly and yields long-lasting memories. Moreover, the behavioural principles and neural circuits that underlie this form of learning are well characterized, allowing an unprecedented analysis of the relationship between neuronal activity and learned behaviour.

Neuronal correlates of aversive memory The search for the neurophysiological mechanisms of aversive memory began in the early 1960s with the observation that an auditory stimulus that was paired with an electric shock modified auditory-evoked field potentials in cats and rats. Other investigators observed changes in late components of cortical potentials that were attributed to a general state of fear, but these changes were not associative (that is, they did not reflect a specific CS–US association) because they occurred in response to both the CS and a

novel stimulus. Therefore, it became clear that field-potential recordings would not be sufficient to identify loci of fear memory.

To address this issue, Olds and his colleagues assessed the latency of conditioned single-unit responses in various brain areas in an appetitive auditory conditioning task. They reasoned that structures showing the earliest increases in auditory responses (in terms of milliseconds after CS onset) were probably primary sites of plasticity, whereas those showing longer-latency changes were probably downstream sites that were involved in the expression of learned responses. Short latency plastic responses (within 40 ms of tone onset) were observed in the posterior thalamus, medial geniculate nucleus and auditory cortex, indicating that these areas might be primary sites of plasticity. They showed that plasticity in subcortical structures could occur independently of the cortex, and indeed, learning related plasticity might not even require the forebrain under some circumstances. In the most systematic neurobiological analysis of Pavlovian learning so far, Thompson and colleagues found that although hippocampal neurons show considerable plasticity during eye-blink conditioning, hippocampal plasticity is not essential for this form of learning. In fact, neuronal plasticity in the cerebellum is crucial for the acquisition and expression of eye-blink conditioning.

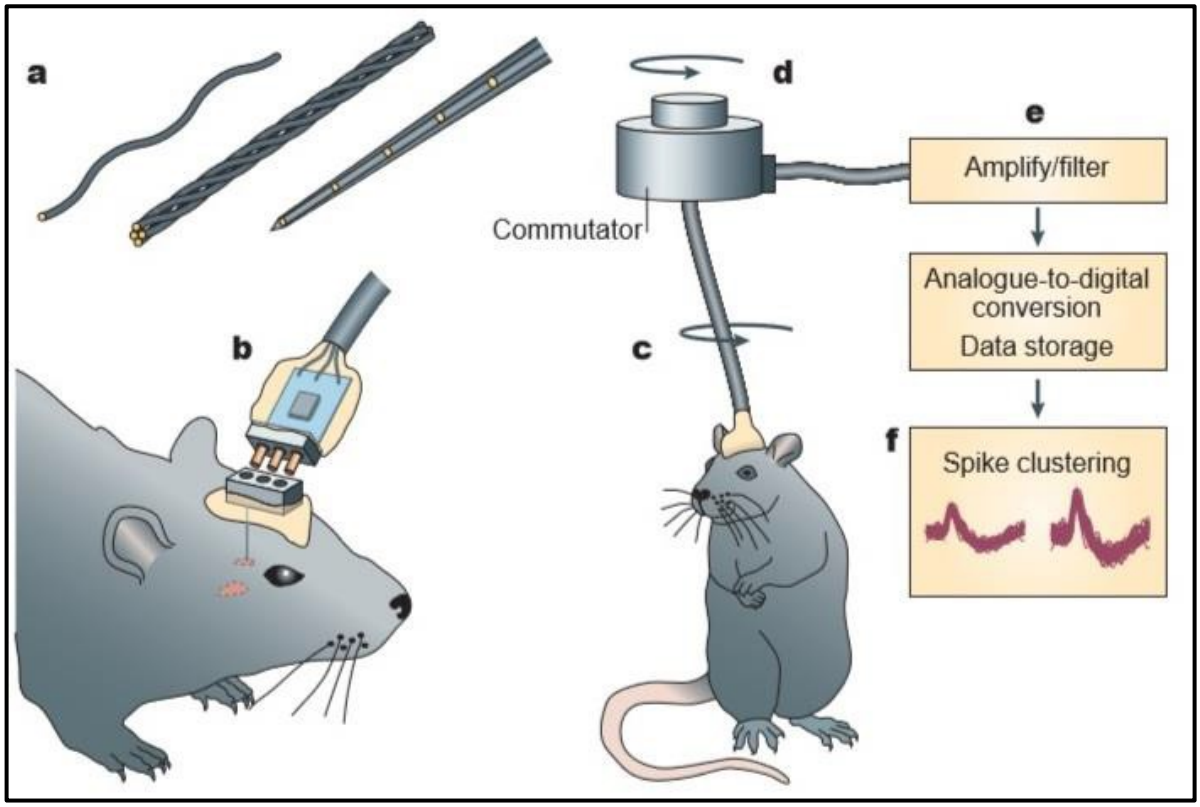


Figure (2): ***Parallel advances in computing hardware (for example, data storage capacity and processor speed) software (for example, neuronal data acquisition and spike sorting) and electrode technology have coalesced to yield powerful multichannel single-unit recording systems for behaving animals. In a typical system, recording electrodes consist of bundles of single wires, multi-wire Stereotrodes or TETRODES, or thin-film silicon arrays (a).Electrode assemblies are either chronically implanted in brain tissue or affixed to moveable micro drives, some of which have been engineered to independently drive up to 16 tetrodes (64 channels) (b).Voltages recorded on each electrode are typically passed through integrated circuits in source-follower configurations that are mounted near the animal's head (a head-stage) to convert neuronal signals into low-impedance signals that are less sensitive to cable and line noise (c).Signals are then fed from the head-stage through a commutator to allow free movement of the animal and cable assembly (d).Neuronal signals are amplified, band-pass filtered and digitized (e).Once digitized, spike waveforms on each electrode channel are sorted into single units using sophisticated clustering algorithms (f). The isolation of single units using such***

methodology varies widely and depends on several parameters. Most importantly, multichannel electrodes, such as tetrodes, seem to yield the most reliable single-unit isolation. Several commercial packages are available to acquire neuronal signals from high-density recording systems, although most electrophysiologists use a combination of home-made technology and commercial products.

Fear and Related Plasticity in the Lateral Amygdala

It is clear that Amygdala was notably absent from all of these earlier studies of fear related response. The thalamus and cortex were thought to be the sites that most probably encode emotional associations and the amygdala was suspected to have a role in modulating memory storage in these areas. However, an influential study by Kapp and co-workers showed that lesions of the central nucleus of the amygdala prevented heart-rate conditioning in rabbits20, consistent with central nucleus modulation of fear-expression centres in the midbrain and hypothalamus.

Subsequent single-unit recording studies of the central nucleus revealed associative plasticity indicating that the amygdala might be a site of plasticity in fear conditioning. Converging on a similar conclusion, Le Doux and co-workers discovered direct projections from the auditory thalamus to the amygdala in rats, and determined this projection to be vital for auditory fear conditioning. Specifically, the lateral nucleus of the amygdala (LA) receives direct projections from the medial subdivision of the medial geniculate nucleus and the adjacent thalamic posterior

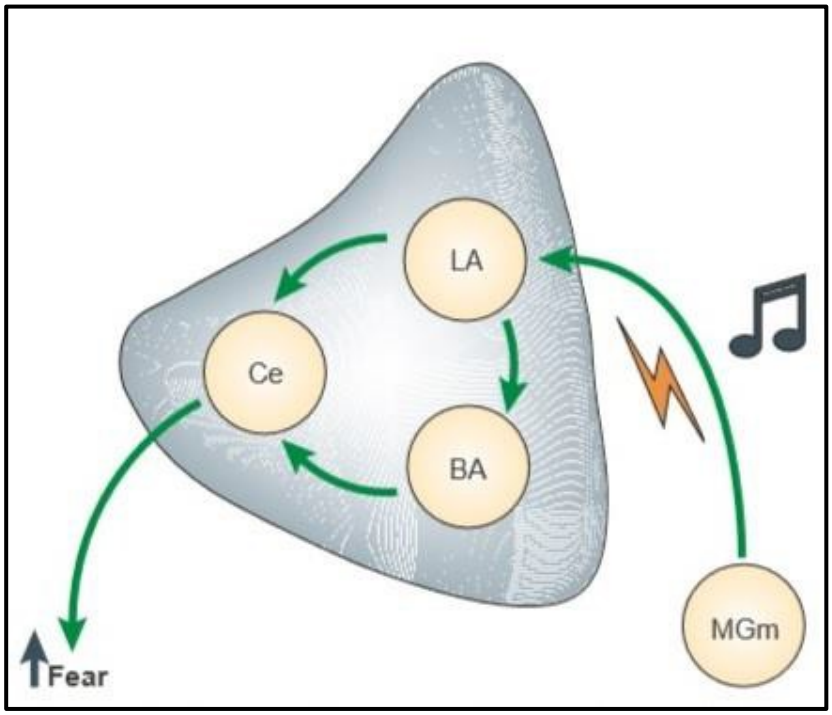


Figure (3): ***This figure shows the neural circuits that are necessary for auditory fear conditioning. Tone and shock inputs from the medial subdivision of the medial geniculate nucleus (MGm) converge in the lateral amygdala (LA), resulting in potentiation of auditory responses of LA neurons. The LA projects to the central nucleus of the amygdala (Ce), both directly and indirectly by way of the basal amygdala (BA). Descending outputs of the Ce to brainstem and hypothalamic structures trigger fear responses.***

intra-laminar nucleus (MGm/PIN), and it relays this information by way of the basal Amygdaloid nuclei to the central nucleus28–31 (FIG.1).Small lesions of the LA or the MGm/PIN prevent fear conditioning, whereas large lesions of the auditory cortex or striatum do not indicating that thalamo–amygdala inputs are sufficient for conditioned fear responses. This finding galvanized interest in the LA as a potential site of plasticity in fear conditioning, and set the stage for the next 15 years of work on the role of the amygdala in this form of learning. Indeed, considerable research now indicates that the amygdala is necessary for both the acquisition and expression of Pavlovian fear memories, but not for all forms of aversive memory.

Subsequent single-unit recording studies in cats and monkeys showed conditioning-induced changes in evoked spike activity in several brain areas, including the midbrain, thalamus and cortex. These changes seemed to be associative because they were not observed during pseudo-conditioning, in which the CS and US were unpaired.

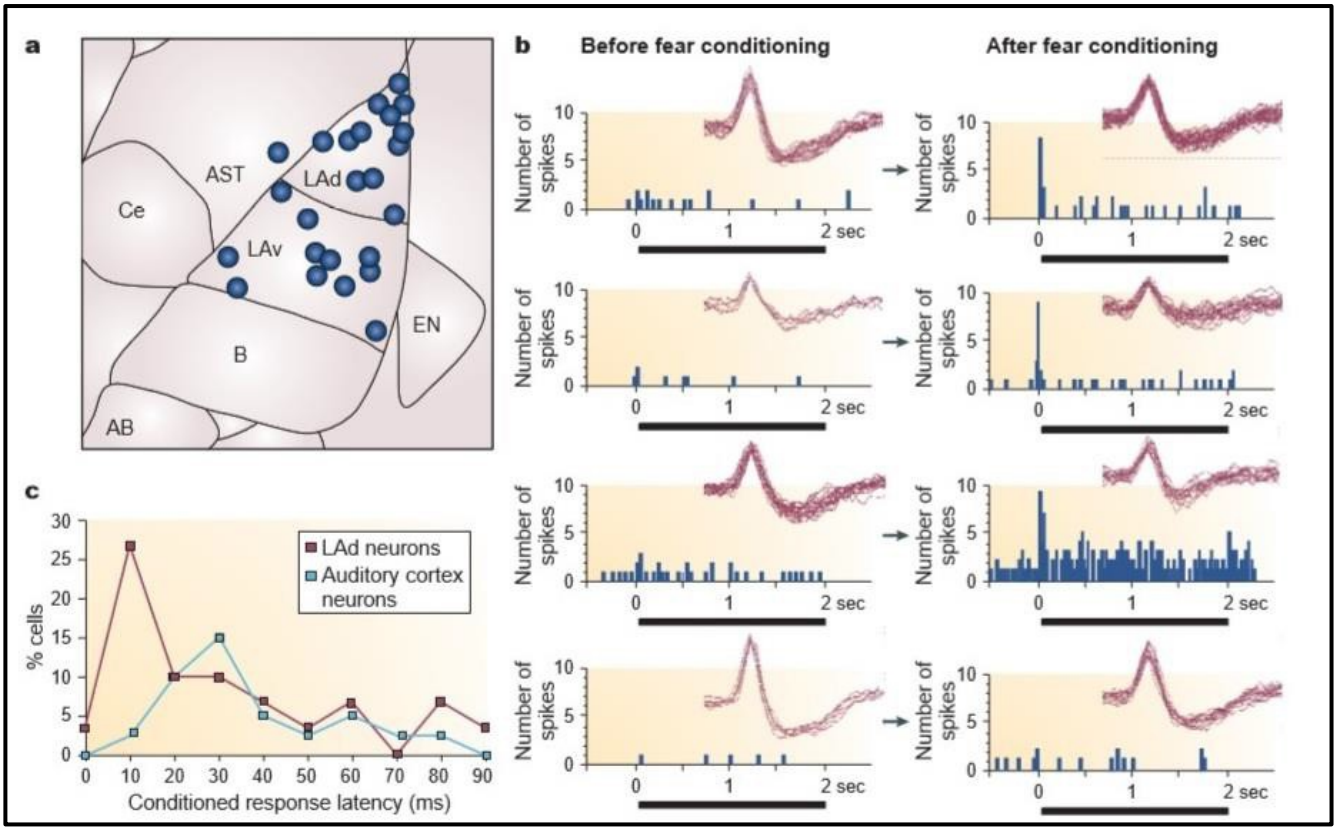


Figure (4): ***Effects of fear conditioning on lateral amygdala neurons. Fear conditioning induces increases in conditional stimulus (CS)-evoked spike firing in lateral amygdala (LA) neurons. a | Electrode placements in the dorsal (LAd) and ventral (LAv) divisions of the lateral amygdala. AB, accessory basal nucleus; AST, amygdalo-striatal transition zone; B, basolateral nucleus; Ce, central nucleus of the amygdala; EN, endopiriform nucleus. b | Peri-event time histograms from eight simultaneously recorded single units in the LA. Each histogram represents the sum of ten CS presentations (black bar) before or after fear conditioning. Representative spike waveforms for each unit are shown as pink lines in the insets. c | Neurons in the LAd show conditioned increases in spike firing at shorter latencies (from CS onset) than do auditory cortical neurons.***

Associative coding in the amygdala For any conditioning-induced change in neuronal activity, it is essential to determine whether the change is related to the associative learning that encodes the CS–US contingency or whether it represents a non-associative process (a form of learning that does not depend on a CS–US association) that is consequent to associative learning, and changes in behaviour to the CS– relative to the pre-conditioning baseline are taken as an index of non-associative sensitization. Of course, the CSs must be chosen carefully to avoid generalization between the cues, which would mask the different associative strengths of the CSs.

Localizing Fear Memory

Fear conditioning increases the responses of single lateral amygdala (LA) neurons to the conditional stimulus (CS). However, this observation alone is not sufficient to imply that LA neurons signal fear memory. Additional criteria (all of which are met by the LA) are as follows:

1. **Is plasticity in the LA associative?**
   Yes. LA neurons increase their tone responses during conditioning in contrast to pseudo conditioning (unpaired tones and shocks).Increases are specific to stimuli that are paired with a shock (CS+),and are not seen with unpaired stimuli (CS–).Does plasticity in the LA depend on plasticity in the auditory cortex? No. Plasticity in the LA precedes plasticity in the auditory cortex, both within and across training trials.
2. **Does plasticity in the LA depend on plasticity in the auditory thalamus?**
   Probably not. Inactivation of the LA with the GABAA (γ-aminobutyric acid, type A) agonist Muscimol prevents the development of plasticity in medial geniculate inputs to the LA. Therefore, plasticity in the medial geniculate nucleus seems to depend on plasticity in the LA.
3. **Do LA neurons learn as fast as the rat learns?**
   Yes. Across trials, plasticity in the LA develops as fast as — or faster than — conditioned fear responses.
4. **Is plasticity in the LA caused by fear behaviour?**
   No. Plasticity in LA neurons can be dissociated from freezing behaviour, implying that LA neurons signal the strength of the conditional–unconditional stimulus association rather than fear per se.

Fear not: Amygdala Inhibition after Extinction

Fear memories enable us to anticipate and respond to dangers in our environments. However, when signals for aversive events no longer predict those events, fear to those signals subsides. This inhibitory learning process, known as extinction, has important clinical relevance as a treatment for anxiety disorders, such as panic disorder and post-traumatic stress. Being able to quantify such aspects of fear along with corresponding aspects of pain associated to the thalamus via such invasive experimental procedures may result in an important breakthrough in

this field of study. Importantly, the inhibitory memories that are learned during extinction compete with the excitatory memories that are formed during conditioning, thereby suppressing fear responses78.Although fear subsides after extinction, and the fear memory is not erased.

In fact, the inhibitory memories of extinction are relatively short-lived and context-dependent. This means that extinction is expressed only in the context in which extinction was given, and even in that context, fear responses will spontaneously recover over time. This transience and context dependence of extinction implies that biology has deemed it better to fear than not to fear. There is considerable interest in understanding the neurobiological mechanisms of fear extinction, and substantial progress has been made in recent years. As for fear conditioning, the amygdala seems to have a vital role in the extinction of learned fear. Pharmacological manipulations that inhibit neuronal activity or disrupt the cellular processes that underlie synaptic plasticity in the amygdala impair extinction.

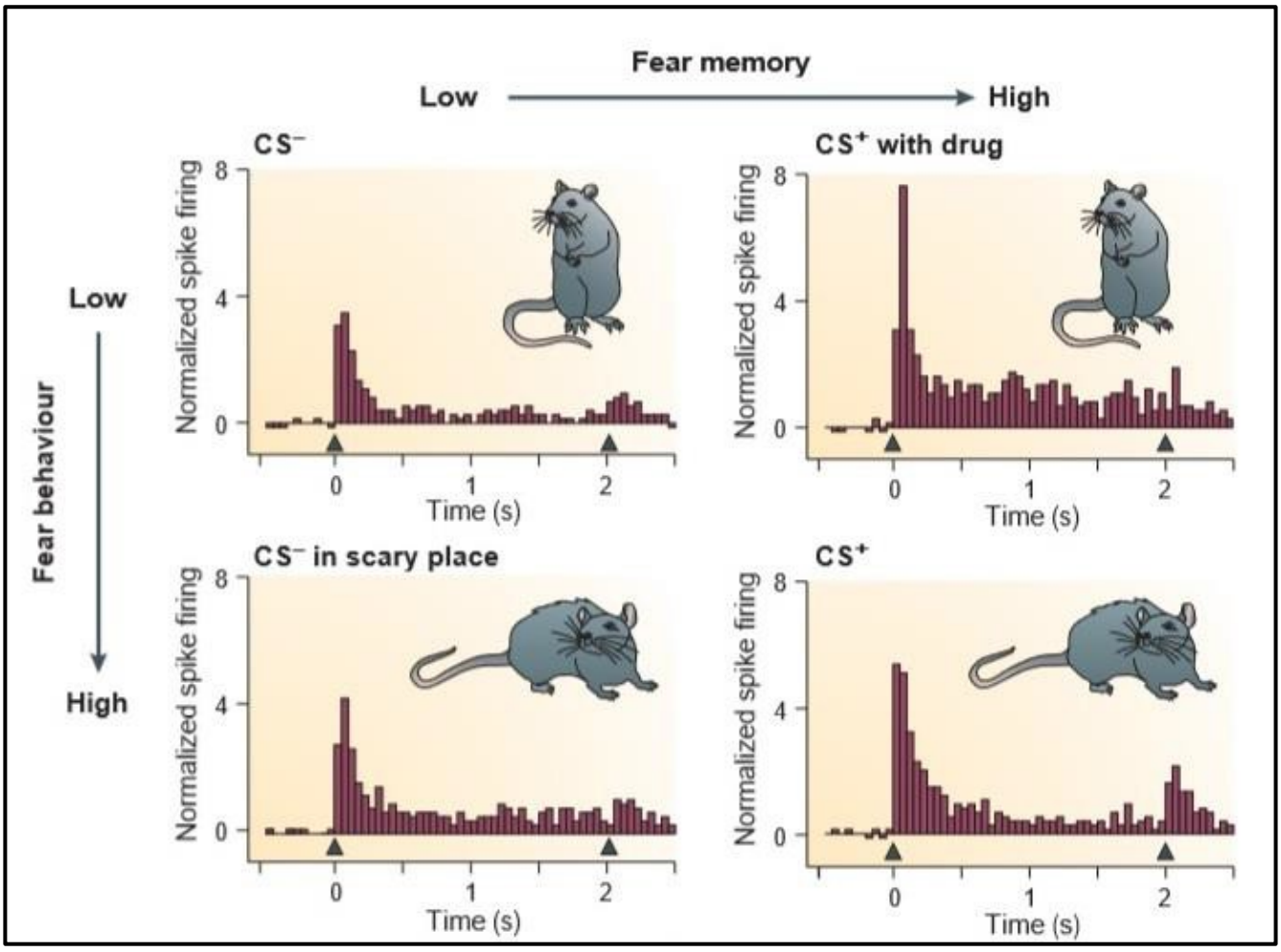


Figure (5): ***Each panel shows population averages for single units recorded in the lateral amygdala (LA) during presentations of an auditory cue paired with a foot-shock (CS+) or an auditory cue that has never been paired with a shock (CS–). Onset and offset of the auditory CSs are indicated by arrowheads. Fear conditioning increases both CS-evoked spike firing and freezing behaviour to the CS+ (bottom right), but not to the CS– (top left). This typical correlation between the associative history of the CS and freezing behaviour can be broken by testing a CS– in a context that has been paired with unsignalled shock (CS– in scary place; bottom left) or by testing a CS+ after inactivating the central nucleus of the amygdala (CS+ after drug; top right). In these cases, the CS– is presented against a background of high fear behaviour, or the CS+ is presented to animals that are***

not capable of showing conditioned fear responses. Nonetheless, LA neurons continue to show activity patterns that are consistent with the associative history of the CS– and CS+; that is, LA neurons represent fear memory, and are not biased by the performance of fear responses

The mediation of extinction by the amygdala is also manifested in the firing of LA neurons. Presenting the CS in the absence of the US reduces the expression of both behavioural CRs and CS-evoked spike firing in most LA neurons. However, not all LA neurons reduce their firing after extinction, and even neurons that do reduce their firing continue to show the synchrony that is fostered by conditioning. This implies that even after extinction, residual traces of conditioning persist in the activity patterns of LA neurons. The reduction in CS-evoked spike firing in the LA that accompanies extinction correlates with the attenuation of fear CRs to the extinguished CS. However, as described earlier, fear extinction is context-dependent and is primarily expressed only in the extinction context. This raises the question of whether the suppression in LA spike firing after extinction is also context-dependent. To address this question; Hobin and colleagues used an elegant within-subjects behavioural design to observe the activity that is elicited in LA neurons by extinguished CSs that are presented either within or outside their extinction context.

Similar studies with respect to pain and plasticity in the thalamus in connection with the amygdala has been recently carried out by Sylvia M. Gustin, Chris C. Peck and others. They used both invasive procedures on rats along with FMRI studies on humans to arrive at conclusive results that help understand pain and plasticity in an analogous manner. It clearly highlights the role of the thalamus in connection to the amygdala in the study of pain using the same procedure as highlighted above.

Conclusion

Numerous studies have revealed both the important works discussed above and current experiments therefore aim at integrating the two for a more holistic quantitative study of the logarithmic brain with respect to its localized centres of emotion. On one hand studies have clearly shown, electrophysiological correlates of memory in neuronal activity patterns of behaving animals, but few of these studies have established causality between learning-induced changes in neuronal activity and behaviour. Recent work in fear conditioning and pain study renews the promise of localizing neuronal activity patterns in the mammalian brain. LA and those of the thalamus seem to be the origin of associative plasticity that is relevant for both learned behavioural responses with respect to pain and fear and physiological plasticity in other brain regions after aversive conditioning.

While on the other hand, multiple studies with respect to the logarithmic scale of the brain and the Bayesian-optimal model have clearly shown, that in order to be best adopted to the environmental conditions on planet earth, one's internal representation should be well matched statistically to the outside world. So that's exactly what we've asserted earlier as our optimization principle in which the logarithmic nature gives the brain certain evolutionary advantages with respect to its environment. Now one of the key factors in evolution of any species for that matter has been the evaluation and response to threat. In this context fear and

pain are vitally important emotional perceptions that contribute to survival and threat elimination. Therefore, in this context it is primarily essential for us to utilize the discussed experimental procedures to understand and verify experimentally, the logarithmic and Bayes-optimal nature of the brain with respect to pain and fear.

Such study is only possible by combining these two approaches in a technical manner with the help of extracellular electrode-based recording on rats with respect to foot-shock and white noise in both the regions of their Amygdala and thalamus. Moreover, modulation of the fear memory code in the Lateral Amygdala is involved in the suppression and renewal of fear responses after extinction. But the issue with respect to medical treatment of PTSD and other anxiety related disorders is quantifying the stress levels with respect to the internal representation of fear, pain etc. of the patient's brain.

Hence, this research opens up new avenues to investigate how the Thalamus and amygdala interact and represent pain and fear. It also helps quantitatively study the storage and retrieval of associated fear memories with respect to a mathematical model. It promises an opportunity to understand how cellular and synaptic mechanisms encode inhibitory extinction memories together with excitatory fear memories. The central role for amygdala neurons in both processes reveals a common target for clinical interventions for anxiety related disorders that might be of vital importance to the future of medical treatment of such disorders.

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