The neurobiological basis of fear: a concise review

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Abstract
Anxiety disorders are amongst the most common psychiatric disorders affecting approximately 25% of all adults. Fear and anxiety have many shared neuroanatomical and neurochemical characteristics. In this paper we refer to a) fear conditioning, (i.e. after a harmless and an aversive stimulus have coincided, the harmless stimulus encountered on its own will cause fear), b) the fear response, including the effects on the hypothalamo-pituitary-adrenal (HPA) axis, c) sensitization, which refers to a general hyperresponsivity of the fear circuits, d) fear memory, and e) extinction, the new learning that the harmless stimulus no longer forecasts a threat. The role of the amygdala and long-term potentiation (LTP) are discussed. Possible anatomical correlates of anxiety disorders and different therapeutic modalities, including the novel drug D-cycloserine, are briefly discussed.

Key words: Fear, Anxiety, Conditioning, LTP, Extinction

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Introduction

It is vital that an organism feels fear in a dangerous situation. The fear reaction helps an animal to survive the present danger, for example by freezing, and thus not attracting a predator's attention. Feeling fear also helps to predict future threats if the animal learns to associate certain innocent stimuli with danger. For example, a specific odour may signal the presence of a predator, enabling the animal to escape before the predator is too close. However, it is also important that organisms can learn as situations change, and innocent stimuli no longer predict danger. When fear persists although there is no danger, precious physical and mental resources are squandered. Anxiety and anxiety disorders may possibly result.

In this paper we discuss the neurobiological basis of fear, with reference to a) fear conditioning, i.e. after a harmless and an aversive stimulus have coincided, the harmless stimulus encountered on its own will cause fear, b) the fear response, including the effects on the hypothalamo-pituitary-adrenal (HPA) axis, c) sensitization, which refers to a general hyperresponsivity of the fear circuits, d) fear memory, and e) fear extinction, the new learning that the harmless stimulus no longer forecasts a threat. We conclude with a few points regarding selected anxiety disorders and different therapeutic modalities.

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The neuroanatomy of fear and fear conditioning

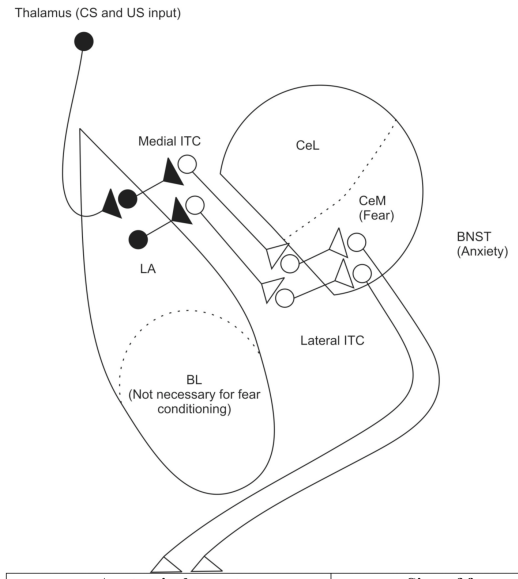
The fear pathways have been widely studied - initially through animal experiments and more recently through brain-imaging studies in humans.[1] The amygdala is the fear centre of the brain[1,2] and fear-inducing stimuli can reach the amygdala either directly through monosynaptic projections from the sensory thalamus to the amygdala or indirectly, i.e., from the sensory thalamus via the cortical association areas to the amygdala.[3] The direct pathway leads to rapid reactions to relatively simple unprocessed perceptual information.[3] The indirect pathway has a longer latency period and delivers information analyzed in terms of different sensory modalities and context.[3]

During Pavlovian fear conditioning, a neutral stimulus (known as the conditioned stimulus, CS) is paired with an aversive unconditioned stimulus (US), and thereafter the organism responds with fear when being confronted with the harmless stimulus (CS) alone.[1,2] Commonly, rats are exposed to a tone (CS) and then receive a foot shock (US). Thereafter, they react with fear and freeze when they hear the tone, even if no shock is given.[1,2] The fear response is not learned and is not voluntary. It is an innate, species-typical response to threat that is expressed automatically in the presence of appropriate stimuli.[2] Fear conditioning thus allows new threats to automatically activate innate ways of responding to danger.[2] Fear conditioning can occur after only one pairing of the CS and US, and can last a lifetime.[1,2]

The fear centre of the brain, the amygdala, is subdivided into various subnuclei. Three of these nuclei, the lateral (LA), basolateral (BL) and the central nucleus, which has a medial (CeM) and lateral (CeL) part, are generally considered important elements of the fear circuit.[4] The LA and BL are composed of both

excitatory glutamatergic pyramidal-like cells and inhibitory GABA (-amino-butyric-acid) cells.[4] A mass of intercalated cells (ITC), which consists of inhibitory GABA-interneurons only, resides between the LA/BL and the Ce.[5] Pare et al. have developed the model described below, after taking into account recent experimental data, e.g., that fear conditioning can occur even after ablation of the BL and that there is no direct connection between the LA and CeM.[5] According to the model of Pare incoming sensory information, including conditioned (CS) and unconditioned stimuli (US), are relayed from the relevant sensory modalities to the thalamus.[1,2] From the thalamus there is an excitatory glutamatergic input to the LA, that synapses on other glutamatergic neurons, which activate the inhibitory GABA cells of the medial ITC.[5] These cells then inhibit the more lateral ITC cells, which in turn are less effective at inhibiting the cells in the CeM which project to the brain stem and hypothalamus to give rise to the fear reaction.5 Thus, activation of the LA results in disinhibition of the CeM, with a resultant fear response, as illustrated in Figure 1. While the CeM is important for fear, the bed nucleus of the stria terminalis (BNST) is implicated in anxiety, i.e. a sustained state of apprehension without an immediate environmental threat.[3,6] The BNST, a set of cell groups situated near the hypothalamus, receives information about stressful situations from the amygdala, hippocampus and cerebral cortex.[7] In the BNST the information is integrated and directly forwarded to several hypothalamic nuclei – especially to the paraventricular nucleus of the hypothalamus (PVNh).[7]

Figure 1: How an emotional stimulus leads to fear
Figure 1 is an amalgamation of the figures of Pare and Walker.[4,6] An emotional stimulus reaches the thalamus via the relevant sensory modalities. Glutamatergic excitatory neurons activate more glutamatergic neurons in the lateral nucleus of the amygdala. These activate medial ITC inhibitory GABA neurons, which in turn inhibit the output of the more lateral inhibitory ITC cells. The output of the medial central part of the amygdala is therefore disinhibited, and activates the various anatomical targets with resultant signs of fear or anxiety as given in the table.



Anatomical target	Sign of fear or anxiety
Lateral hypothalamus	Tachycardia, galvanic skin response, paleness, pupil dilation, blood pressure elevation
Dorsal motor nucleus of vagus Nucleus ambiguus	Ulcers, urination, defecation, bradycardia
Parabrachial nucleus	Panting, respiratory distress
Ventral tegmental area Locus coeruleus Lateral dorsal tegmental nucleus Basal forebrain	Behavioural and EEG arousal Increased vigilance Increased attention
Nucleus reticularis pontis caudalis	Increased startle
Central gray	Freezing, hypoalgesia
Trigeminal, facial motor nerve	Facial expressions of fear
Paraventricular nucleus (hypothalamus)	Corticosteroid release (also see Figure 2)
Other aminergic brain stem nuclei	Mood and activation state of brain

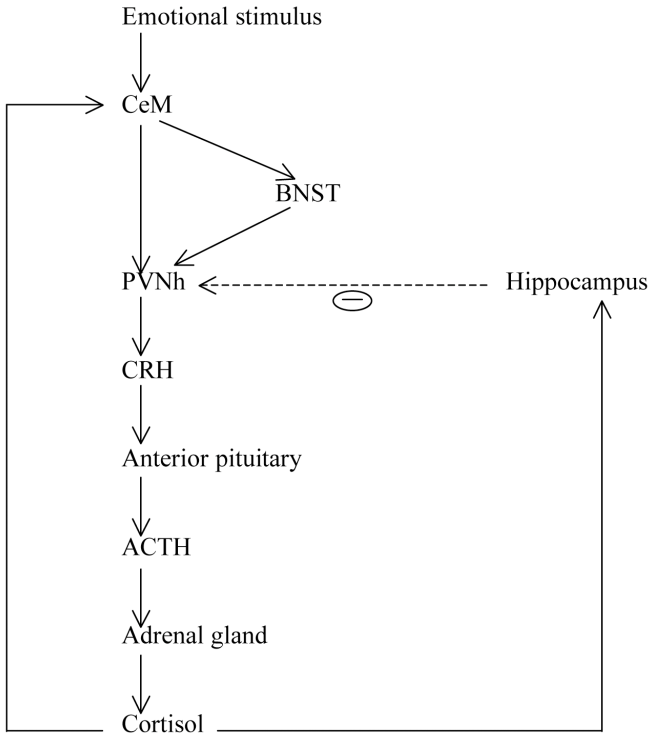
: glutamateric excitatory neuron
: GABA inhibitory neuron

The fear response: effect on the hypothalamo-pituitary-adrenal axis (HPA-axis)

Expression of the fear response is largely mediated through information sent to the hypothalamus and brain stem. Some of the anatomical targets in the brain stem and hypothalamus, as well as the signs of fear and anxiety, which are triggered by the CeM and/or BNST are listed at the bottom part of Figure 1. A strategic relationship exists between the HPA-axis, the amygdala and the hippocampus with regard to the fear response. This relationship is briefly discussed in the next paragraphs and summarized in Figure 2.

When an aversive emotional stimulus activates the CeM and/or BNST, as shown in Figure 1, the CeM and/or the BNST activate the paraventricular nucleus of the hypothalamus (PVNh), which releases corticotropin releasing hormone (CRH).[1-3] CRH then acts on the anterior pituitary, stimulating the release of adrenocorticotrophic hormone (ACTH), which in turn causes the adrenal glands to release cortisol.[1,3,8] Increased levels of cortisol then further stimulate the CeM/BNST to act on the PVNh to further increase cortisol release. This relationship between the CeM/BNST

Figure 2: The effects of emotional stimulation on the HPA-axis
An emotional stimulus activates the CeM or BNST as shown in Figure 1. The paraventricular nucleus of the hypothalamus (PVNh) secretes CRF, which prompts the secretion of ACTH by the anterior pituitary. ACTH triggers the secretion of cortisol by the adrenal gland. Cortisol has a feed-forward activation of the CeM, enhancing the stress reaction. Cortisol, however, also acts on the hippocampus, which inhibits the release of CRF by the PVNh.



on the one hand and the HPA-axis on the other thus represents a positive feedback system[1,2,8], which, if allowed to continue, would have dire physiological, as well as psychological, consequences.

The HPA-axis, and by implication cortisol secretion, is controlled by negative feedback to the pituitary, the hypothalamus and the hippocampus with the hippocampus representing the primary negative feedback regulatory mechanism.[9] The way the HPA-axis hyperactivation during aversive conditions can be curtailed, is through cortisol's actions on the hippocampus, which then inhibits further CRH release from the PVNh.[1-3] However, with severe or relentless stress, the stress hormones lead to glucose depletion in the hippocampal cells, making them sensitive to damage by excess glutamate.[1,2,8] The functions which depend on the hippocampus, including the control of the HPA-axis thus become compromised.[1-3] In such a situation, activation of the HPA-axis continues, with detrimental results on functions such as declarative memory consolidation and spatial recall.[1-3] The purpose of the stress response is to mobilize resources in the short run.[1,2] This continued activation of the HPA-axis is one of the major mechanisms through which long-term relentless stress may predispose individuals to disease.[1,2]

The molecular basis of fear conditioning

Learning is made possible through neural plasticity, i.e. the ability of neurons to be altered through experience. Hebb's axiom states that ''neurons that fire together, wire together''.[1,10] The molecular basis of fear conditioning is long-term potentiation (LTP), which is briefly discussed below.[1,2]

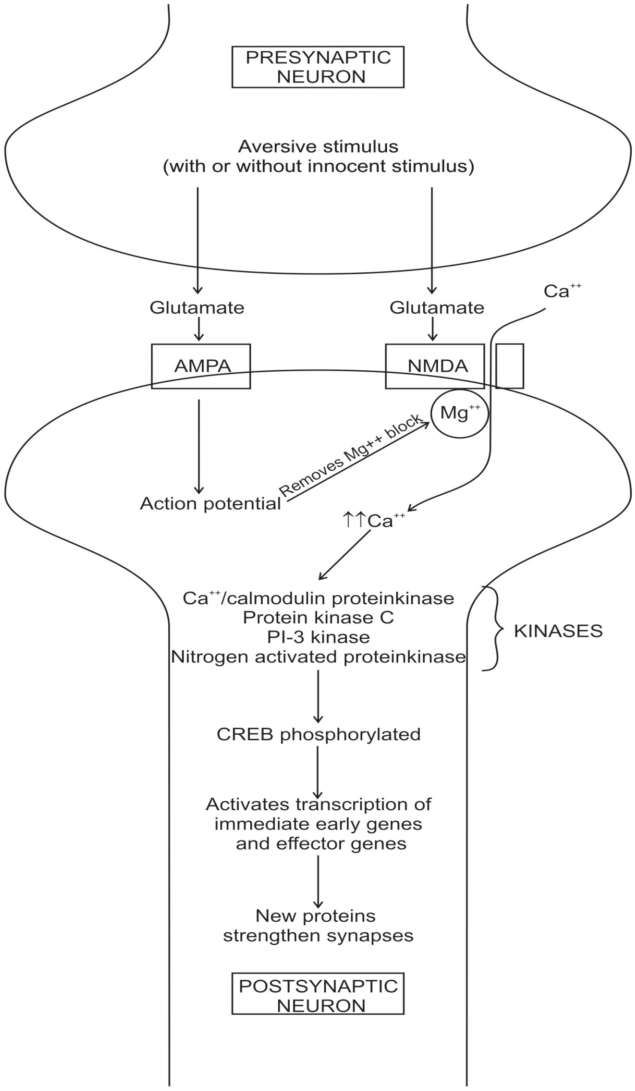
Normally, the intracellular rest potential in the LA is even more negative than in other cells, due to tonic inhibition by GABA.[1,2,11] Neutral stimuli, which by definition do not signal danger, therefore can not elicit an action potential and therefore not trigger the fear response.[1,2,11] Sufficiently aversive stimuli, however, cause the release of enough glutamate by the presynaptic cell to activate the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxaloeproprionic acid) receptor and cause an action potential.[1,2,11,12] The action potential removes the Mg^{2+}-block from the NMDA (N-methyl-D-aspartate) receptor, allowing the entry of Ca^{2+} into the postsynaptic cell.[1,2,11] Increased Ca^{2+} intracellularly activates a variety of kinases, which trigger gene activation that result in the formation of new proteins that strengthen the synapses between the pre- and postsynaptic neurons.[1,9,10] This is known as LTP.[1,2,11,12] This very synoptic generalised description of LTP is diagrammatically presented in Figure 3.

If a neutral (CS) stimulus happens to coincide with an aversive (US) stimulus, the synapses between the neurons transmitting the neutral stimulus and those of the fear pathway are also strengthened.[1,2,11] This accounts for fear conditioning, i.e. the ability of an innocent trigger to unleash the fear reaction – particularly conditioning that occurs below conscious level where impulses are transmitted via the direct pathway from the thalamus to the amygdala.[1,2,11] Conditioning that involves higher cognitive processing of fear depends on plasticity of both the amygdala and cortex.[1-3,11]

Sensitization

The fear pathway of some people is known to be hyperresponsive, however, it is not yet well understood why this sensitization of the fear pathway may occur.[3] Harmless stimuli may lead to large postsynaptic responses, i.e. a strong activation of the fear response, due to both presynaptic and postsynaptic changes.[1,3,13] Sensitization

Figure 3: The molecular basis of LTP
An aversive stimulus reaching the presynaptic neuron of the LA triggers the release of glutamate, which binds to an AMPA receptor on the postsynaptic cell and gives rise to an action potential. Glutamate also binds to NMDA receptors with no effect, until the action potential removes the Mg2+ block allowing the entry of Ca2+ into the cell. Increased intracellular Ca2+ activates various kinases, which then phosphorylate CREB (cyclic AMP response binding element), which activates the transcription of various immediate early genes and effector genes. New proteins are thus synthesized which strengthen the synapse. If an innocent stimulus happens to coincide with the aversive one, LTP also results with regard to the innocent stimulus, thus giving rise to fear conditioning.



probably occurs in response to genetic and environmental factors. One example of a recently identified genetic component is that persons with one or two copies of the short allele of the serotonin transporter promotor polymorphism exhibit greater amygdala neuronal activity, and more anxiety.[14]

The environment is also important, especially during times of rapid (or crucial) neurodevelopment in early life.[15-17] Immature stress-responsive systems are highly plastic, and future responses to stress are programmed during the prenatal and early postnatal periods.[15,18] Stress early in life, e.g. in the case of childhood abuse, may lead to a persistent sensitization of fear circuits to even mild stress, and so establish the basis for anxiety disorders in adulthood.15 During favourable mother-infant interactions, a novel stimulus leads to a lower corticoid response and a more rapid

return to baseline due to an increase in the glucocorticoid receptor expression that is involved in the termination of the stress response.[15] Schore has theorized that the interactions between mother and infant become stressful if the mother has a poor ability to comfort and regulate the infant due to structural limitations of her own brain.[15] It is postulated that under such conditions the child will have a greater corticosteroid output in response to a novel stimulus, the increased levels will persist for longer and that the child will develop permanently reduced numbers of the cerebral corticosteroid receptors needed to terminate the stress reaction.[15] This may partly explain the intergenerationally transmitted poor capacity for self-comforting obvious during times of stress.[15]

Fear memory

The way fear memories are stored is of importance to clinicians, both in order to understand many symptoms of anxiety disorders, and to grasp how psychotherapy works. We refer to the work of le Doux[1], Joseph[10] and Schore[15] to describe possible mechanisms by which fear memories are laid down.

Two factors are central to the understanding of fear memory. The first is the difference between implicit emotional memory encoded by the amygdala and explicit declarative memory laid down by the hippocampus.[1,15] The second is the fact that emotional aspects of fear memories are said to be stored in the right hemisphere, while the narrative version of what happened during the fearful episode is stored in the left hemisphere.[1,15]

The infant amygdala is able to lay down emotional implicit memories.[10,15] However, explicit declarative memories are dependent on the hippocampus, which myelinates later.[10,15] This contributes to childhood amnesia, which is the inability to consciously recall events of infancy and early childhood.[10,15] Another contributing factor to childhood amnesia is that the corpus callosum, which allows for interhemispheric communication, only myelinates around age 5.[10,15] Before age 5, emotional memories are stored in the right hemisphere, without a corresponding narrative version being encoded in the left hemisphere.[10,15] Children who experience abuse usually have no one to turn to for help, and thus no way of finding words for what happened.[10,15] The period of childhood amnesia is generally longer for those who were severely abused as children.[10] Adults who experienced childhood abuse thus often have strong emotions of fear below conscious awareness, but no words to explain (even to themselves) where these emotions originated.[15] A major purpose of psychotherapy is to enable the patient to lay down a narrative version of the trauma.[15]

Another reason for poor explicit memory of traumatic events is that during severe stress, high levels of corticosteroids are toxic to the hippocampus and impair its function of laying down declarative memories.[10,15] This may explain the fragmentary quality and amnesia of extremely traumatic events, even when experienced in adulthood.[10,15]

Explicit fear memories initially depend on LTP and the hippocampus, but after a few hours to days are stored in long-term memory.[16-18] Here the fear memories are quiet, below the surface of conscious awareness, until something related to the fear provokes the fear response.[19,20] This trigger may be a loud noise, e.g. a back-firing car, which reminds and ex-soldier with PTSD of gunfire, unleashing a fear reaction.[1] The trigger may even be internal. For example, patients with panic disorder may develop a chronic anticipatory anxiety that they will have a panic attack. If their heart rate increases for an innocuous reason, like climbing stairs, this may set off a panic attack, because the tachycardia formed part of their previous panic attacks.[3,21] Patients with panic disorder often develop agoraphobia because they keep away from all unfamiliar things for fear of being triggered into panic.[13,21] Thus generalized avoidance may replace the avoidance of true danger.[22]

Having discussed how innocuous stimuli can trigger fear through sensitization or conditioning, and how these memories are stored, the next paragraphs will deal with extinction, i.e. the process by which fears can be controlled.

The neuroanatomy of extinction

It is critical for survival to adapt to changing environmental conditions. If a previously conditioned stimulus no longer predicts danger, it is imperative that an organism learns not to react with fear any longer. Failure to learn that previous fears are redundant may result in psychopathology, as discussed in the next section.

Extinction normally occurs when a CS is repeatedly encountered without an US, e.g. in rodents, when the tone is repeatedly heard without a foot shock following.[1,4] It has been conclusively shown that extinction does not erase fear conditioning, but rather replaces it with new learning, i.e. that the CS no longer predicts danger.[1,4,20,23,24] The newly learnt CS-no danger association then competes with the previous CS-US association.[20,23,24] Extinction is context-dependent, which means that a previously extinguished fear may reappear in a different situation.[20,23,24] Also, previously extinguished fears may spontaneously reappear when the individual is under stress.[20,23,24]

The prefrontal cortex includes the lateral prefrontal region, which is important for working memory, the orbital frontal cortex, which is involved in emotional decision making, and the medial prefrontal cortex.[4] These three regions are interconnected.[4] The lateral prefrontal cortex, the classic working memory area, does not have connections to the amygdala, but the orbital and medial prefrontal cortices (especially the anterior cingulated region) do.[1] The dorsal prefrontal region therefore has some indirect access to the amygdala through the other regions.[1] The infralimbic part of the medial prefrontal cortex (mPFC) is responsible for extinction, with the hippocampus providing contextual constraints.[4,20,23,24] It is not clear at present exactly how the mPFC inhibits the amygdala, and two models have been proposed. The first is by Pare and Quirk, who propose that the mPFC affects all ITC cells at all levels equally, thus producing inhibition of CeM cells.[5,25] The second model is by Grace and Rosenkranz, who suggest that the mPFC activates inhibitory interneurons within the LA and BL.[26] These models are not mutually exclusive, and both may be valid.[19,21] The mPFC thus serves as a link, enabling the cognitive processing system in the prefrontal cortex to regulate the emotional processing by the amygdala.[1] Animals with abnormalities of the mPFC seem to experience fear and anxiety in (objectively seen) safe situations, which is reminiscent of humans with pathological anxiety.[1]

Therapeutic approach

Various therapeutic approaches to anxiety disorders exist. We refer very briefly to psychotherapy and drugs. Anxiety disorders are difficult to treat successfully with insight orientated psychotherapy alone.[1] It can be speculated that this may be because, to our present knowledge, no direct connections exist between the lateral prefrontal cortex and the amygdala.[1] This could explain why behavioural therapy, which is less dependent on insight and is more dependent on the development of new habits (i.e. implicit learning), may be more successful in some types of anxiety disorders.[1]

Drugs can promote adaptation and learning of neural circuits.[1] Patients can benefit most when therapy guides the drug-induced adaptivity of their brains in a sensible way.[1] Drugs commonly used include selective serotonin reuptake inhibitors (SSRIs) and the benzodiazepines (BZs).[1] It seems that both act by facilitating the inhibitory effects of GABA in the amygdala, thus making it more difficult for glutamate to elicit excitation at its postsynaptic receptors.[1] Thus, fearful stimuli are less likely to activate the amygdala and elicit a fear response.[1] Furthermore, SSRI's have been shown to increase the amount of serotonin available at serotonin receptors, stimulating these receptors for longer periods of time.[1] As a result, a stronger intracellular response is generated leading to enhanced gene activation and protein synthesis providing neurotrophic support to the synapse.[1] Long-lasting effects of drugs may thus result from neuroplastic changes in the functionally integrated fear circuit.[1]

A novel drug which has been shown to be safe in humans, and might be useful to aid in the extinction of fears is D-cycloserine (D-4-amino-3-isoxazolidone).[27,28] D-cycloserine is a partial agonist at the NMDA-receptor and if combined with extinction therapies, may facilitate the new learning that the conditioned stimulus is not linked to danger.[27,28] The advantages of D-cycloserine include the finding that it exerts a generalized extinction of fear (i.e. not so context-dependent), and that there will therefore be less chance of relapse under stress.[27] Disadvantages are that it must be given for short periods in conjunction with desensitization therapies, and that it does not work with concurrent antidepressant use (because chronic treatment with antidepressants can alter activity at the NMDA receptor level).[27]

Conclusions

The amygdala, especially the basolateral and central nucleus of the amygdala is central to the fear reaction. While the central nucleus of the amygdala, through its effects on nuclei of the brain stem and hypothalamus, appears to be fundamental to the expression of the symptoms of fear, the BNST, which integrates information about aversive events from various brain regions, including the amygdala, is implicated in anxiety. Early exposure to danger can lead to fear conditioning, which is an important protective mechanism. However, when a previously conditioned stimulus no longer predicts danger, it is imperative that an organism learns not to react with fear. New drugs are becoming available to aid in psychotherapeutic treatment of unwarranted fear-related phenomena. Whilst promising, further study is required. In conclusion the words of Francis would appear appropriate: ''Very often what we consider to be abnormal patterns of development are entirely understandable in terms of adaptations to adversity in early life''.[29]

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