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REVIEWS

# Amygdala: Neuroanatomy and Neurophysiology of Fear

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**Abstract**—This review is devoted to neuroanatomical and neurophysiological mechanisms of Pavlovian fear conditioning with a focus on the amydgalae, two subcortical nuclear groups, as primary structures responsible for controlling conditioned fear responses, and synaptic plasticity at their afferent and efferent projections as a cellular mechanism to mediate the formation and retention of fear memory. We survey current data on anatomical organization of the amygdaloid complex, as well as on its afferent and efferent projections and their functional significance. A special consideration is given to auditory inputs to the amygdala to analyze the mechanisms of aversive conditioning to sensory (acoustic) stimuli.

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*Key words*: amygdala, fear conditioning.

## INTRODUCTION

At present, it is generally believed that fear represents an indivisible basic emotional reaction which arises in the event of danger to adapt an individual to an existing situation. Fear mobilizes an organism for the realization of the following behaviors: freezing, avoidance, aggression etc. [1]. Most of studies indicate that fears can be extremely diverse both in quality and intensity.

In addition to evolutionarily developed and genetically programmed, i.e. innate (unconditioned) fears, for example, of pain, loud noises, light [1–4], there are fears acquired during life. In contrast to innate fears, acquires fears are a consequence of individual experience. They help orientate in permanently changing environment, recognize/assay the degree of danger and take measures to neutralize/minimize adverse factors. Fear is thought to be caused by a real or imaginary (experienced though as a real) danger which threatens individual lives, ideals, principles, values etc.

Fear as an emotion is one of the most important triggers of defensive behavior, both individual and social. Regulation disorders of this process and the possibility of its manifestation in a variety of pathological forms make all studies concerned with unraveling the fear mechanisms extremely topical. In the International Classification of Diseases (ICD-10) anxiety and fear disorders are classified as "Phobic anxiety disorders" (F40). This group includes the disorders which share as a sole or prevailing symptom a fear (phobia) of specific situations that offer no real danger. The word "phobia" derives from the Greek "phobos", i.e. fear, horror, and in specialized literature this term is defined in

different ways. For example, O.V. Kerbikov et al. offer the following brief definition: "Phobia is an obsessive fear" [5]. American psychiatrists G. Kaplan and B. Sadock believe that phobia represents a persistent irrational fear resulting in a conscious avoidance of a specific fear-eliciting object, activity or situation [6].

A phenomenology of fear can be explored by different aspects of its expression. For example, philosophers address fear as a metaphysical process in an attempt to reveal its fundamental, spiritual or existential elements, while psychologists and sociologists treat fear as psychological and social processes trying to disclose its empirical regularities, to determine the peculiarities of its emotional experience in different individuals and society as a whole as well as the factors promoting its enhancement or attenuation.

Although these and many other approaches are very exciting and fruitful, a deeper insight into the mechanisms of fear requires its neurophysiological principles to be investigated. For this purpose, experimental animal models (mainly rodents, rats and mice) are usually employed. The data obtained therein are often apprehended or even interpreted in terms of the paradigm which was elaborated by psychologists to describe emotions of human beings. The validity of such an interpolation is subject of debates, but it is typically justified by the fact that anatomical substrates responsible for the genesis of emotions exhibit a striking similarity and a high degree of phylogenetic conservatism both in humans and animals [7]. It is not the fear realization mechanism *per se* but just a system of its cognitive regulation and control that undergoes evolutionary changes. Phylogenetically, the latter emerged and developed as a cortical superstructure aimed to ADAPT the performance of the limbic system (including amygdala) not so much to ambient stimuli as to evolving organism's behavior which becomes ever more sophisticated [8]. Meanwhile, archaic reactions and their physiological mechanisms may remain intact, but the degree of their afferent control depends on the evolutionary status of an organism. The observations made on patients with traumatic brain injuries or organic pathologies, as well as MRI examinations, indicate a similarity between neurobiological mechanisms of fear in humans and animals [9–12].

## THE CONDITIONED-REFLEX NATURE OF FEAR AND ITS "ANATOMICAL" LOCALIZATION

A conditioned reflex concept is most productive principle to understand and study the fear formation and realization mechanisms [13, 14]. A consideration of fear within this paradigm implies that fear has a conditioned nature and, therefore, exhibits all the properties of conditioned and/or unconditioned reflexes. As any other reflexes, fear may have innate and acquired forms. Innate fears, like unconditioned reflexes, are realized via the genetically determined "stationary" neuroanatomical pathways, whereas acquired fears, like all conditioned reactions, employ *de novo* emerging temporal neural connections. The latter, according to the E.A. Asratian's theory [15], represent a result of interaction between the two unconditioned reflexes, orientative and reinforcing. The former is triggered by a neutral (conditioned) stimulus which elicits only an unconditioned orientative response, while the latter is activated by an aversive (unconditioned) stimulus which initiates an aversive (unconditioned) response "traced" by the cortical structures and experienced at the cognitive level as fear or anxiety. Temporal concordance of these stimuli is assumed to result in the formation of associative neural connections between the centers of these reflexes. At the behavioral level, this process manifests itself as follows: conditioned stimulus presentation elicits an unconditioned reaction which arose previously only in response to an aversive stimulus.

Neurophysiological understanding of the events and processes underlying the above mechanisms was initiated by now classical works of Kluver and Bucy who assessed the effect of bilateral temporal lobectomy on monkey behavior [16, 17]. In these tests, experimental animals exhibited a number of drastic changes in emotional behavior called in the aggregate "psychic blindness" and named subsequently the Klüver–Bucy syndrome. This syndrome manifested itself in the disappearance of fear leading thereby to dramatic changes in the animal herd behavior [17, 18]. Later it was shown that even a local brain lesion confined to bilateral ablation of the amygdaloid complex would suffice for the Klüver–Bucy syndrome [19–21]. Similar

effects were found in other mammalian species [22] allowing a valid suggestion that a leading role in the mechanism of fear belongs to the amygdala, a complex telencephalic structure included in the limbic system.

One of the trailblazers and now a recognized leader in studies of the amygdala and its role in organizing conditioned responses is professor of the New York University Dr. Joseph LeDoux. By common efforts of his and some other research groups it was demonstrated that the amygdala serves not only the hub of unconditioned fear but also a center where associative coupling forms between the conditioned stimulus and the unconditioned response. While the morphological substrate of such a coupling is the predominant convergence of afferent inputs onto the dorsolateral nucleus cells of the basolateral amygdaloid complex, its mediating mechanism is synaptic plasticity. Conditioned response formation was established to be accompanied by changes in the efficacy of synaptic connections in this amygdaloid nucleus [23–26]. This has been shown in our experiments as well. Specifically, it has been established that aversive conditioning to acoustic stimuli led to the occlusion of long-term potentiation (LTP) of the synapses formed by cortical inputs onto projection cells of the amygdaloid dorsolateral nucleus, as well as to the reduction of the paired-pulse facilitation indices [27]. These phenomena indicate that the neuronal mechanism of conditioning and the mechanism of artificially elicited LTP share the same underlying resource. Based on the fact that LTP development and conditioned response formation are accompanied by the fall of the paired-pulse facilitation indices, we may conclude that the mechanisms of these phenomena is underlain by an increase in the likelihood of neurotransmitter release from synaptic vesicles.

## ANATOMY OF THE AMYGDALOID COMPLEX

In view of the extremely significant role of the amygdala in fear formation, anatomical studies of this structure and its projections are of special interest. The term "amygdala" was first coined by the German anatomist Burdach [28] who used it to describe the population of nuclei situated in the human anterior temporal lobe and having the shape which resembles an almond (*Amygdalus communis*). Ever since, the concept of the amygdala as an anatomically isolated structure has been modified and supplemented. Currently, this collective term denotes a complex of nuclei comprising no less than thirteen structures each of which is identified by its specific cytoarchitectonics, histochemistry and extra-/intranuclear connectivity patterns [29]. The amygdala is now described in different vertebrate species including monkeys [30, 31], cats [32, 33], rats [34], turtles [35] and birds [36]. The nuclei comparable to the main amygdaloid complexes of amniotes were also shown in lower vertebrates (anamniotes) [37].

The studies conducted on rats, mice, cats and monkeys indicate that the structure of the amygdala as well as afferent and efferent projections of their nuclei share a striking similarity [38]. It is noteworthy, however, that in the succession of vertebrates from reptiles to humans the afferent basolateral nucleus of the amygdala (BLA) tends to increase relative to its efferent central nucleus (CeA) [7, 39]. Such a relative increase is ascribed to rapid development in these animals of the cortical formations that are closely and reciprocally connected with BLA [7, 39]. Since rodents (rats and mice) are among most commonly used experimental animals, the description of the amygdala in this review is based on the data obtained on these objects.

In literature, several variants of classification of the amygdaloid nuclei in rats are accepted [29, 32, 38, 40–42], but since these differences are insignificant in the context of our paper, we describe the amygdaloid nuclei using the most widespread nomenclature first offered by Price et al. [33] and modified later by Sah et al. [38].

According to this classification, the amygdaloid nuclei are divided into three groups (see Table): **First**—*deep or basolateral group* (sometimes, *basolateral nucleus of amygdala*), includes the lateral (LA), basal (B) and accessory basal (AB) nuclei; **Second**—*superficial* or *cortical group*, consists of the nuclei of the lateral olfactory tract (NLOT), bed nuclei of the accessory olfactory tract (BAOT), anterior and posterior cortical nuclei (CoA, CoP) and periamygdaloid cortex (PAC); **Third**—*centromedial group*, includes the medial (M) and central

Classification of the amygdaloid nuclei [38]

| DN—Deep nuclei<br>BLA—Basolateral nuclei | SN—Superficial nuclei | CN—Centromedial nuclei |
|---|---|---|
| LA—Lateral nucleus:<br>LAdl—dorsolateral division<br>LAvl—ventrolateral division<br>LAm—medial division<br>B—Basal nucleus:<br>Bmc—magnocellular division<br>Bi—intermediate divison<br>Bpc—parvicellular division<br>AB—Accessory basal nucleus:<br>ABmc—magnocellular division<br>ABpc—parvicellular division | NLOT—Nucleus of the lateral olfactory tract<br>BAOT—Bed nucleus of the accessory olfactory tract<br>CoA—Anterior cortical nucleus<br>CoP—Posterior cortical nucleus<br>PAC—Periamygdaloid cortex:<br>PACm—periamygdaloid cortex, medial division<br>PACs—periamygdaloid cortex, sulcal division | CeA—Central nucleus:<br>CeC—capsular division<br>CeL—lateral division<br>CeI—intermediate division<br>CeM—medial division<br>M—Medial nucleus:<br>Mr—rostral division<br>Mcd—dorsal part of central division<br>Mcv—ventral part of central division<br>Mc—caudal division<br>BNST—Bed nucleus of stria terminalis |

(CeA) nuclei and bed nucleus of the stria terminalis (BNST). A special group is composed of the cells of the amygdalo-hippocampal area (AHA), anterior amygdaloid area (AAA) and intercalary neurons which cannot be unequivocally referred to any of the above groups. It is necessary to point out that practically all the amygdaloid nuclei can be further subdivided into smaller structures (divisions) presented in Table.

The currently available data do not allow a definitive conclusion on whether the amygdala is functionally a single whole or represents a constellation of closely spaced but functionally dissimilar nuclear groups. However, the suggestion that within the amygdala there occurs the formation of distributed systems which unite all these separate nuclei for the realization/maintenance of one or another function is finding ever-growing support. Specifically, as some authors believe [38, 43–45], within the amygdala it is possible to isolate the group of nuclei involved in the formation and expression of fear. The morphological substrate which provides connectivity of the amygdaloid divisions and the other CNS levels for the realization of this function is represented by the system of its afferent, efferent and own projections [34, 38, 43–45].

## AMYGDALOID SYSTEM OF AFFERENT PROJECTIONS

The bulk of anatomical evidence on the amygdaloid projection system in animals was obtained using retro- and anterograde tracers (markers) injected into different parts of the amygdala, cortex or subcortical structures [34, 36] as well as the methods of local destruction, stimulation or application of transmitters and/or their agonists/antagonists [38]. Each amygdaloid nucleus receives specific afferents from several telencephalic and diencephalic structures. Most widespread are sensory inputs both from the thalamic nuclei and cortical fields. The largest sources of multisensory afferents in the amygdala are the prefrontal cortex, hippocampus and parahippocampal structures (perirhinal and entorhinal cortex, subiculum). The generalized diagram of these afferents and specific innervation of individual amygdaloid nuclei are presented in Fig. 1.

Knowledge of the amygdala's anatomy and connectivity enables the analysis of *how the information about conditioned and unconditioned stimuli is processed* in the amygdala. Most comprehensively these principles were analyzed for auditory inputs. Yet in the mid-80s of the past century, LeDoux et al. [47, 48] showed that main sources of auditory afferents in the amygdala are the medial division (MGm), posterior intralaminar (PIN) and suprageniculate (SG) nuclei of the diencephalic medial geniculate body (MGB). Later, it was established that auditory information can reach the amygdala via two independent pathways. One of them is a straight pathway via thalamo-amygdala projections; the second, indirect, is via thalamo-cortical-amygdala projections [49]. Both cortico- and thalamo-amygdala inputs are presented by glutamatergic fibers. The former enter the amygdala together with the fibers of the external capsule [50]

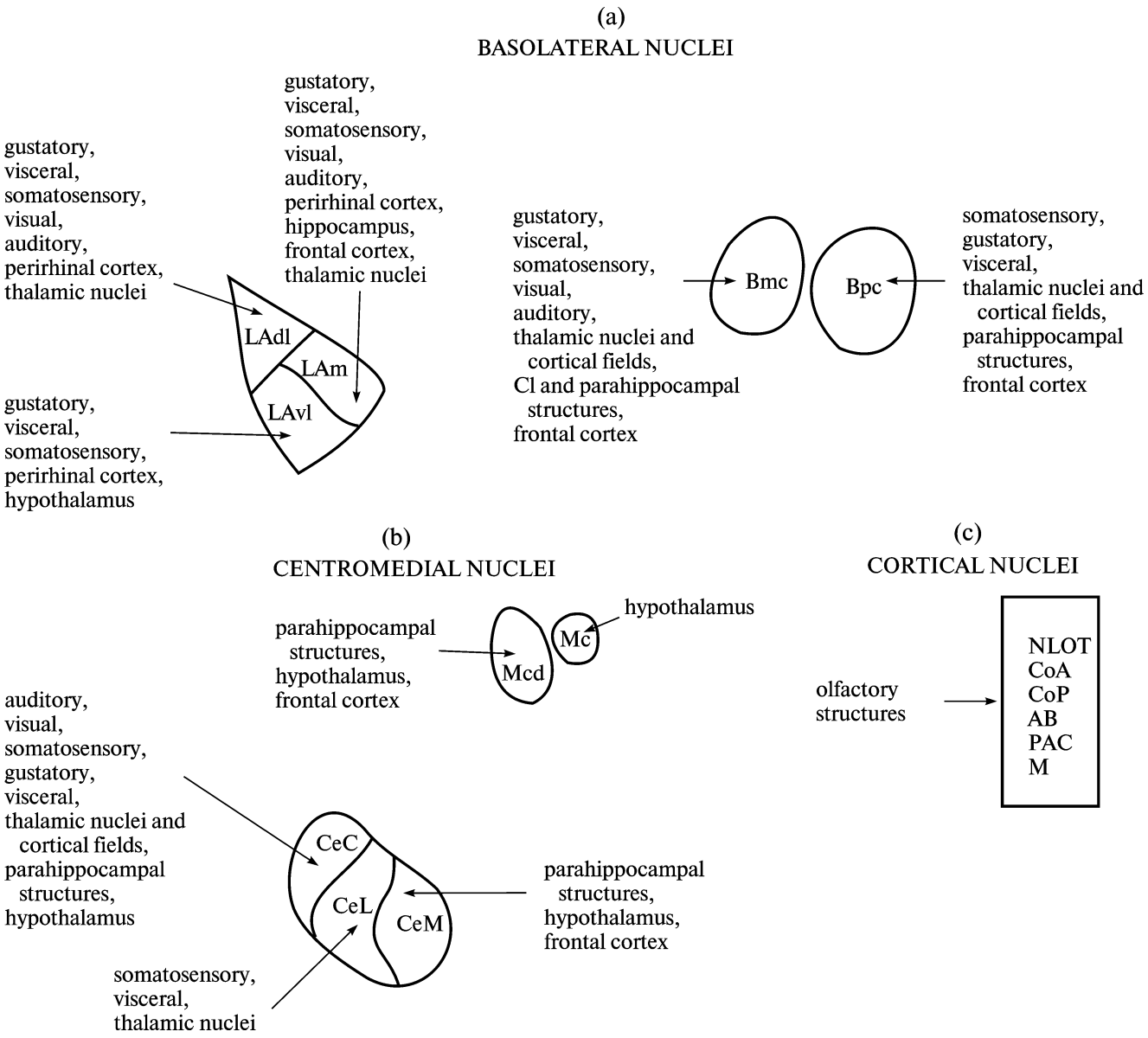


**Fig. 1.** Generalized scheme of main afferent inputs to the amygdala [38]. (a) Afferents of basolateral nuclei; (b) afferents of centromedial nuclei; (c) afferents of cortical nuclei. Here and in Figs. 2–3: abbreviations deciphered in Table 1.

while the latter—from the internal capsule [38]. Information coming along thalamo-amygdala pathway originates from the above-mentioned MGB substructures while thalamo-cortico-amygdala pathway includes, in addition to them, the ventral (MGv) and dorsal (MGd) nuclei of the medial geniculate body.

Both tracts, thalamo-amygdala and thalamo-cortico-amygdala, end on neurons of the same amygdaloid nuclei. Meanwhile, the highest density of endings of thalamic and cortical auditory afferents was detected in the dorsal (Ladl) and medial (Lam) divisions of the lateral nucleus (LA) [46, 51–53].

It is also worth mentioning that each of the above pathways alone, either thalamic or cortical, is quite sufficient for fear conditioning to a simple acoustic stimulus. Total disruption of auditory fear conditioning results only from simultaneous lesion/blockade of both tracts [49]. This indicates

that sensory information influx to the amygdala via at least one of these pathways is a requirement for fear conditioning [47, 49, 54]. Presumably, main difference between thalamo-amygdala and thalamo-cortico-amygdala circuits is that the former represents a "fast response" channel which communicates to the amygdala most operating, though least detailed, so-called "framework" information. The thalamo-cortico-amygdala channel, in turn, delivers more detailed information [55], but the rate of its delivery is much lower because this channel includes accessory thalamocortical relays necessary for more sophisticated information processing at the cortical level. Thus, we may suggest that the presence of the two concerted information channels indicates their complementarity. Namely, the thalamo-amygdala channel compensates the low speed of the thalamo-cortico-amygdala pathway, whereas the latter makes up for low-detailed information conducted by the thalamo-amygdala pathway. Obviously, such a complementarity allows optimization of the speed-accuracy trade-off in information processing.

Information of other sensory modalities comes to the amygdala in the similar way (Fig. 1) [38]. Thus, via the suprageniculate thalamic nucleus afferents the lateral amygdaloid nucleus receives, in addition to auditory, somatosensory and visual signals [56]. Furthermore, visual inputs follow along the lemniscal and extralemniscal pathways. The former begins in the lateral geniculate body, then relays in the primary and secondary visual cortex and follows to the posterior temporal field TE2 which mediates its entry to the amygdala. Along the extralemniscal pathway visual information reaches the amygdala through the thalamic pulvinar which receives inputs from the superior colliculus [57].

The visual system, like the auditory, was shown to be involved in aversive associative conditioning which implies that combination of light flashes with painful electroshock leads to a sustained aversive response to previously neutral light stimulus [58].

In visual perception studies using functional magnetic resonance imaging (fMRI) it was shown that the human brain is distinctive in a high sensitivity of the amygdala to such extraspecific visual stimuli as faces [9]. The main center of processing the signals of such a high level is the gyrus fusiformis cortex at the base of the temporal lobe (fusiform face area) [10, 11]. Animal experiments enabled the reconstruction of the pathway along which this information can reach the basolateral amygdala in the human brain. It turned out that the main structure that provides input from the areas homologous to the above-mentioned is the lateral entorhinal cortex. It is likely that in humans and animals analysis of information about varied (not only visual) vitally important stimuli occurs herein. This suggestion is supported by the fact that the same cortical area provides the amygdala with olfactory afferents as well [12]. Moreover, there is evidence of the involvement of the entorhinal cortex in contextual fear conditioning [59].

It should be noted that a common feature of the overall sensory afferentation of the amygdala is that most part of the information about a conditioned signal arrives to this structure not from the projection thalamic nuclei or primary fields of the sensory cortex but mainly from the thalamic structures of the extralemniscal system and associative cortical areas [38, 60].

The involvement of the amygdala in the genesis of fear responses implies that cells of its nuclei receive information about both conditioned and unconditioned stimuli. The afferent pathways delivering the latter type of information were examined most thoroughly in the nociceptive system. Pain, or nociceptive, responses may be evoked by the stimulation of nociceptors with strong mechanical, thermal, chemical, light and other irritants. Nociceptive information comes within the spinothalamic tracts to the posterior group of thalamic nuclei from where it is transmitted to the somatosensory and insular cortical fields. The amygdala receives this information both from the thalamic level, specifically from the intralaminar nucleus (PIN) [61], and the above-mentioned cortical fields [46, 53]. Experimental destruction of brain areas showed that elimination of the thalamic posterior intralaminar nucleus (PIN) is not sufficient enough to block fear conditioning to a painful stimulus [61, 62]. Total inability to form such associations arises only upon a combined destruction of the insular cortex and PIN. The latter observation indicates that information about both

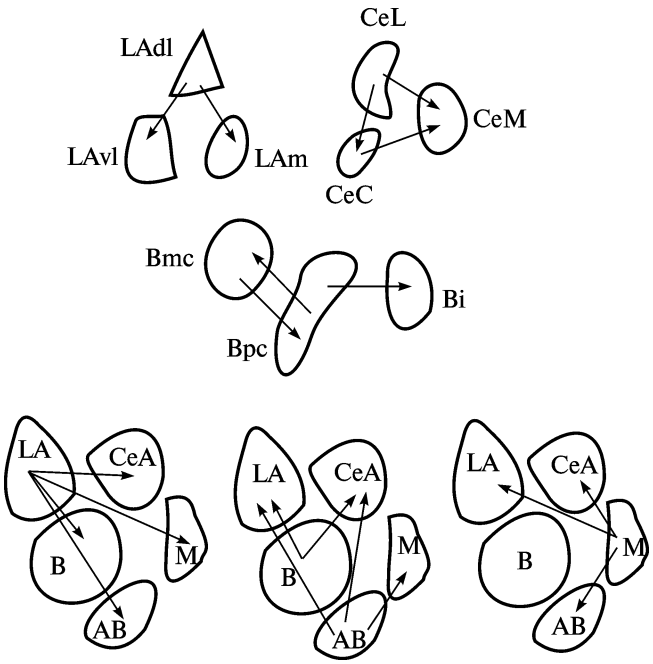


**Fig. 2.** Generalized scheme of main intra- and interamygdaloid projections.

unconditioned and conditioned stimuli comes to the amygdala along the two pathways: direct (thalamo-amygdala) and indirect (thalamo-cortico-amygdala). It appears that both tracts mutually complement one another and optimize nociceptive information processing.

## AMYGDALOID SYSTEM OF INTRA- AND INTERNUCLEAR PROJECTIONS

The system which provides intra-amygdaloid processing of sensory information is composed of intra- and internuclear projections. A generalized diagram of internuclear projections of the basolateral and centromedial groups is presented in Fig. 2. Separate nuclei and subnuclei of the centromedial group are connected mainly with each other but not with other amygdaloid divisions. Subnuclei of the basolateral group, in addition to internal connections, project to the central nucleus.

Complex organization of intra- and internuclear projections is a key aspect of this structure's performance which determines the implication of its neurons in a wide variety of functions. This can be well exemplified by inhibitory neurons in the CeA nucleus among which two subpopulations with mutually antithetic functions were singled out [7, 63, 64]. The first group includes so-called $CeL_{off}$ cells which are inhibited when an arbitrary signal is followed by an unconditioned stimulus. The second group comprises $CeL_{on}$ neurons which, on the contrary, are activated under the same conditions. Using molecular-genetic labeling it was demonstrated that the first group of cells synthesizes protein kinase C δ-isoform ($PKC\delta^+$) while the second group lacks it ($PKC\delta^-$). Both cell types form reciprocal connections and can inhibit each other. A study of $PKC\delta^+$-neurons revealed that this cell type is included in several distributed systems and participates in the realization of diverse functions of the amygdala. Combination of behavioral methods and state-of-the-art ontogenetic approaches enabled the demonstration that $PKC\delta^+$ neurons are implicated in the regulation both of feeding behavior and anxiety [7]. Photostimulation of $PKC\delta^+$ neurons bearing the light-sensitive ChR2 protein built in their membrane reduces the anxiety level [65] and suppresses feeding behavior [65]. Reversible inhibition of these neurons by the stimulation of the built-in hM4Di G protein-coupled receptors leads to the activation of feeding behavior [65]. The anxiety reduction is believed to occur due to anxiogenic signals form BLA and neuronal projections from CeL to CeM and BNST [66, 67] while the appetite reduction results from anorexigenic signals from BLA, parabrachial nucleus (PBN) and insula (IN) [65]. Noteworthy are the interesting features of the interaction of $PKC\delta^+$ ($CeL_{off}$) and $PKC\delta^-$ ($CeL_{on}$) neurons with each other and projection BLA cells [63, 64]. The function of $PKC\delta^-$ ($CeL_{on}$) neurons is associated with freezing maintenance both in response to the presentation of an aversive stimulus and the emergence of a related conditioned signal. $PKC\delta^+$ ($CeL_{off}$) and $PKC\delta^-$ ($CeL_{on}$) neurons receive inputs from BLA; however, on-cells respond with a shorter delay allowing them to inhibit off-neurons due to reciprocal projections. Upon presentation of an aversive or related arbitrary signal, this pattern of intranuclear projections enables triggering of a freeze response and a suppression of the other amygdala's functions mediated by the activation of off-cells.

As another example of the local intra- and internuclear regulatory system we can offer the system

of intercalary neurons residing in the amygdaloid dorsolateral nucleus. These interneurons form inhibitory GABAergic synapses within the amygdaloid dorsolateral nucleus [68] and are involved in the regulation of sensory information flow converging on the soma of projection neurons. They can block, completely or partially, long-term potentiation (LTP) of synapses formed by cortical or thalamic afferents on projection neurons of the amygdaloid dorsolateral nucleus [69]. At the same time, the inhibitory effect on LTP was found to manifest itself differently in cortico- and thalamo-amygdala synapses. Such an asymmetry in the local inhibitory control is due to the fact that synapses formed on interneurons by inputs from the thalamus have the larger quantum bumps than those from the cortex [69]. The latter finding serves an additional demonstration of the complexity of intra-amygdaloid projections and regulation which forestalls behavioral responses including fear.

During analysis and processing of sensory information within the amygdala a pattern of afferent activity forms which determines phenomenological expressions of fear.

## AMYGDALOID SYSTEM OF EFFERENT PROJECTIONS

The amygdaloid efferent system can provide the realization of different fear components (physiological, behavioral or psychological) due to its connection with the executive brain systems. The nuclei of the basolateral complex (BLA) play a certain role in this process. Supposedly, direct projections of this nucleus to the dorsal striatum affect behavioral strategy, those to the hippocampus—affect spatial memory, while those to the orbitofrontal cortex—affect emotional memory (Fig. 3) [43, 44]. An important, if not leading, role in fear expression belongs also to the CeA and BNST nuclei which receive multiple inputs from the basolateral complex (BLA) and send, in their turn, efferents to the numerous brain structures mediating fear expression [34, 38, 70, 71]. Supposedly, the more transient processes actually classified as a fear are realized via CeA, while the longer processes classified as an anxiety state are realized via BNST [72].

These nuclei mediate the processes occurring in BLA and determine the activity of those effectory brain structures that elicit fear-specific behavioral and vegetative responses. Presumably, projections to the hypothalamus mediate tachycardia, blood pressure changes, galvanic skin response, skin paling etc., projections to the central gray matter mediate freeze response, pain sensitivity reduction (hypoalgesia) etc., due to projections to the motor nucleus of the vagus nerve (double nucleus) bradycardia, defecation and urination may arise, and so on. With reference to the Davis's review [43, 44], projections of these nuclei as well as effects of their chemical and electrical stimulation are generalized in Fig. 3 [43, 44].

Presumably, the analogous information processing and fear genesis scheme is valid for humans as well. Specifically, this is evidenced by the studies using intravital fMRI which not only enables real-time visualization of brain structures' functional activity, but also demonstrates how this activity correlates with *individual* fear experience and task performance against its background. The results of these studies revealed that fear expression in humans involves the same brain structures as in animals [73, 74]. Specifically, expression of fear elicited by the presentation of genetically determined (innate) or conditioned aversive stimulus (spider, snake, pain) in humans, likewise in animals, is accompanied by bilateral activation of the amygdala and related structures involved in the realization of fear [73].

Community of the fear realization mechanisms in humans and animals was also confirmed by the analysis of visual information pathways to the amygdala. Specifically, using MRI technology it was shown that both in humans and animals visual information arrives to the amygdala both via the fast (thalamo-amygdala) and slow (thalamo-cortico-amygdala) channels. These channels differ not only in the information conduction velocity but in some selectivity as well. For example, in the studies by Sato et al. [9] it was shown that during human face analysis the information about an emotionally significant facial expression comes to the amygdala via the "fast response channels" (i.e. subcortical structures), whereas the information about a neutral facial expression or just an eye gaze arrives to the amygdala via the cortical path-

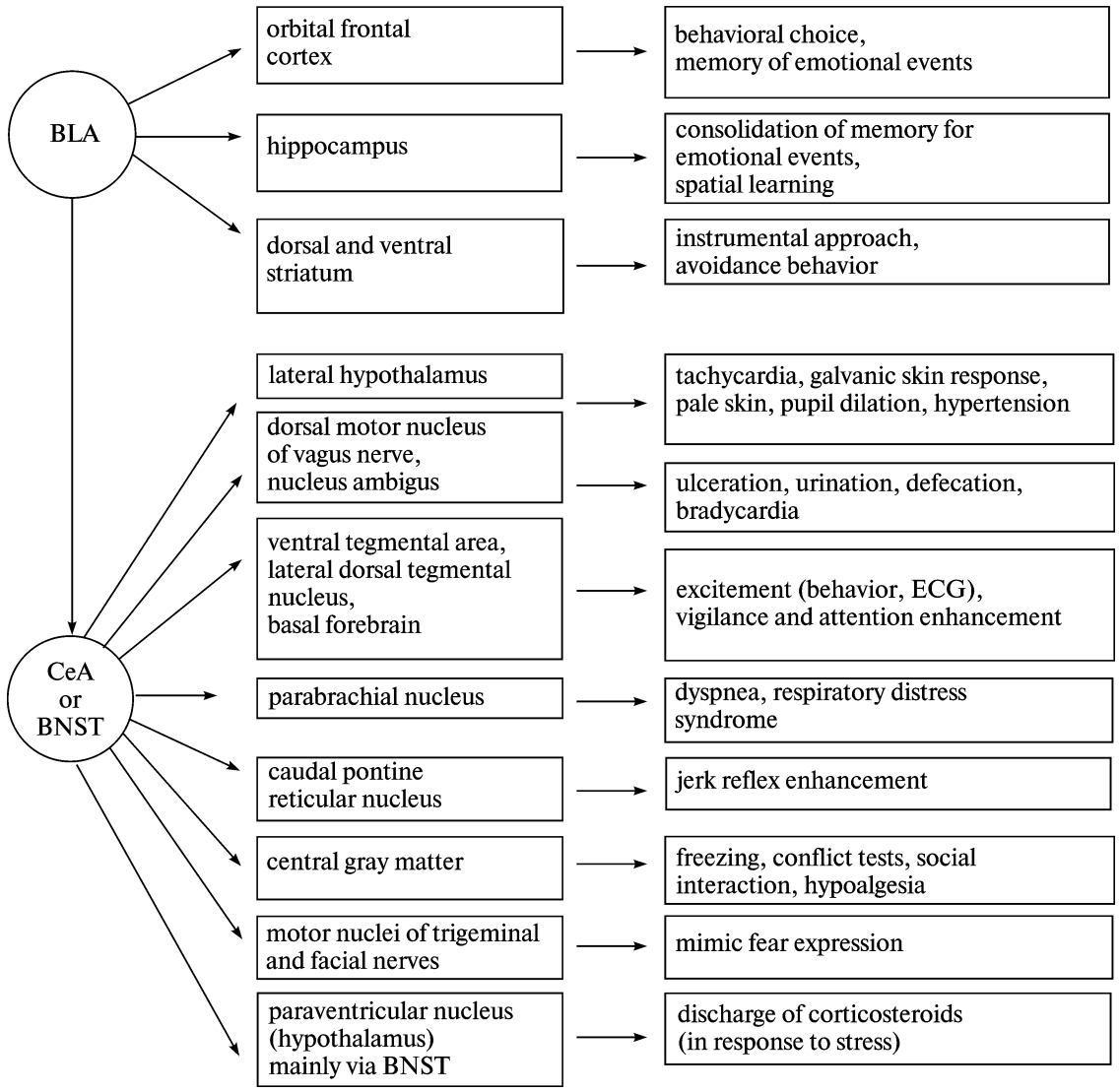


**Fig. 3.** Generalized scheme of main efferents of the amygdaloid nuclei and their putative functions [44].

way which, as suggested above, provides more detailed, though more delayed, information.

Some operational features of the fear expression system were found in humans only in studying the interaction of the amygdala with brain cortical structures. For example, when the human object was presented a stimulus whose potential hazard was preliminarily eliminated by the specialist's explanation, only a left-sided response of the amygdala and related structures was detected [73]. Presumably, such an asymmetry is due to a modulating effect of the prefrontal cortex activated during psychotherapeutic manipulations.

Strong development of the prefrontal cortex is considered a remarkable feature of the human brain. It is this brain structure that is traditionally associated with advanced cognitive abilities distinguishing people from animals. Phylogenetically, this area, together with all the other human brain specific areas and cytoarchitectonic fields, emerges only in primates [8] where it occupies a vast rostral territory of the brain hemispheres, while its larger part has no homologs in rodents [8, 75]. In the prefrontal cortex it is generally accepted to mark out the dorsal, medial and orbitofrontal areas. Among these areas and their separate cytoarchitectonic fields there are numerous reciprocal circuits [76–78]. In addition, the dorsolateral area

receives multiple inputs from the primary sensory fields [79], while the orbitofrontal area—from the secondary sensory and olfactory fields [78, 80, 81].

The orbitofrontal area is closely connected with the amygdaloid nuclei while a part of cortico-amygdaloid efferents project to intercalary neurons unequivocally not included in any conventional nuclear structures [82]. The peculiarity of these neurons is that they have an inhibitory effect on neurons of the centromedial nuclei [83–85] allowing thereby the prefrontal cortex both to activate and inhibit main efferent neurons of the amygdala. Overall, these orbitofrontal cortical projections to the amygdala and dorsolateral prefrontal cortex provide a close interaction of the human cognitive and emotional spheres underlying thereby the unique human abilities to perceive, analyze, describe and classify their fears as well as other emotions. Apparently, the peculiarities of the prefrontal cortical circuits may account for the human ability to experience anxiety and fear in response both to real and mental stimuli as well as to consciously control emotions and related irrational/non-constructive behavior. Due to the interaction with the prefrontal cortex, fear experience in humans may qualitatively differ from that in animals. Human fear represents not only an organism's response but a phenomenon that can be analyzed and consciously modulated. It should be noted, however, that in spite of all these human-specific peculiarities the basis of the fear expressing system remains similar both in humans and animals. In this regard, the development of the cortex and its projections, as well as new possibilities this development begot, may be considered as an extra regulatory superstructure to the conservative and phylogenetically invariable fear genesis system which functions similarly both in humans and animals. Obviously, one of the functions of this superstructure consists in restraining the biological autonomy of fear expression (and emotions in general) and coordinating their correct manifestation within the frames of individual world outlook and in accordance with cultural/social context [8].

## CONCLUSION. ACHIEVEMENTS AND PROSPECTS

The data available presently allow assuming that physiological maintenance of fear responses is realized by a complex, multicomponent, genetically determined brain system which includes, at least, danger detectors and mechanisms triggering behavioral and vegetative expressions of fear, its sensation, memory and association. A key element of this system is the amygdala which receives sensory information about events of the surrounding and cognitive worlds as well as about the state of the organism, processes this information and relays it to the executive (effector) brain centers responsible for fear realization. At the level of sensations this process is experienced as a specific feeling which, being enriched with somatic and visceral sensations, is interpreted at the level of conscience as a fear/anxiety or complex emotions the latter are included in. Since fear can be caused by events both of the real and cognitive worlds, this paradigm does not refute the ideas of cognitivism but consider them as a particular case when e.g. fear is a response to the objects/subject or situation of the imaginary world as well as to itself.

The involvement of the amygdala in these processes determines its functional role as sort of interface or coordination center which orchestrates the performance of the visceral and motor spheres. While C.E. Izard in his differential emotions theory postulates the presence of such a center, in the I.P. Pavlov's theory of classical conditioning it may be considered as a component of the conditioned reflex. An important role in the amygdala's function is attributed to its dorsal nucleus which, apart from serving a sensory-relay nucleus, is involved in the formation of the acquired amygdala-dependent fears. The latter are of the conditional nature and represent one of the associative memory forms. Supposedly, the substrate of such an association is a convergence of multimodal stimuli onto neurons of this nucleus, while its underlying neural mechanism is a long-term plasticity and, specifically, a long-term potentiation (LTP) of the amygdaloid synapses [23–27].

Thus, fear as a psychophysical phenomenon is based on the system which can expand and become more sophisticated during individual development. This process is accompanied by the development and complication of the regulatory, i.e. fear controlling, mechanisms at the higher CNS levels. An increasing role of the higher CNS divisions in onto- and phylogenesis complicates the function-

ing of the fear realization system so much that fear experience passes from the category of objective, i.e. genetically determined emotions independent on the individual experience into the category of events that depend on the previous experience and are considered subjective. Nevertheless, the phenomenology of fear even in human beings and animals is very much alike. This is due to the fact that the anatomical structures and circuits underlying different fear *phenotypes* are very conservative and are little changeable during phylogenesis. The latter enables a comparison of results obtained on animals and their approximation to humans.

Conspicuous progress in this direction has been associated with the development and adoption of genetic and behavioral methods as well as the studies on surviving section and those using EEG and fMRI. Still, many issues remain unresolved. Specifically, it is extremely little known how the CNS higher functions supported by the brain cortical formations may exert a differential effect on fear expression. How does fear differentiation occur? What does determine the leading symptom/symptoms of fear expression? How does the innervation from the other brain areas influence fear expression and how are these influences synthesized and analyzed? What are the mechanisms triggering and modulating individual components of the system providing fear expression?

Currently, high hopes in solving these issues are placed on the methods of noninvasive control of functionally identified neuronal populations developed within the frames of the ontogenetic approach. Already now the existing state-of-the-art techniques enable the use of vector DNA to insert *in vivo* specific genes encoding light-sensitive proteins into the genomes of certain groups of neurons. Being incorporated into the neuronal membrane, these proteins form the light-sensitive channel/receptor complexes which depolarize the neuronal soma and its processes and mediate thereby spike generation upon light activation at appropriate wavelengths.

Remarkably, light stimulation allows the activation not only of the soma of genetically modified neurons but their distal processes as well including axons with synapses they form on neurons of the remote brain structures. The latter determines the wide applicability of such an approach in *in vitro* electrophysiological studies on sections of those brain structure that are spatially remote from the locations of genetically modified neurons (their cell bodies).

Additional prospects of this approach are associated with the development and application of fiber-optic technologies which already now enable selective *in vitro* activation (via the implanted fiber) of the cells pre-transfected with vector DNA. At present, genetic methods allow the simultaneous introduction of proteins with different photosensitivity to different brain areas. In *in vitro* experiments, this makes it possible to differentially activate the required afferent/efferent inputs/outputs by changing the wavelength of the stimulating light and to track the results of this activation in behavioral tests.

The use of light-conducting fibers in concert with physiological, behavioral and classical genetic methods opens unprecedented avenues for studying the function of the brain and its divisions both *in vivo* and *in vitro*. The advent and further development of such an approach may be considered a methodological revolution at the turn of the 20$^{th}$ and 21$^{nd}$ centuries. The results of the novel approach will not take long to wait because the data it promises are of paramount importance both for fundamental and applied science.

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