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Organization of intra-amygdaloid circuitries in the rat: an emerging framework for understanding functions of the amygdala

Asla Pitkänen, Vesa Savander and Joseph E. LeDoux

The amygdala is located in the medial aspects of the temporal lobe. In spite of the fact that the amygdala has been implicated in a variety of functions, ranging from attention to memory to emotion, it has not attracted neuroscientists to the same extent as its laminated neighbours, in particular the hippocampus and surrounding cortex. However, recently, principles of information processing within the amygdala, particularly in the rat, have begun to emerge from anatomical, physiological and behavioral studies. These findings suggest that after the stimulus enters the amygdala, the highly organized intra-amygdaloid circuitries provide a pathway by which the representation of a stimulus becomes distributed in parallel to various amygdaloid nuclei. As a consequence, the stimulus representation may become modulated by different functional systems, such as those mediating memories from past experience or knowledge about ongoing homeostatic states. The amygdaloid output nuclei, especially the central nucleus, receive convergent information from several other amygdaloid regions and generate behavioral responses that presumably reflect the sum of neuronal activity produced by different amygdaloid nuclei.

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THE AMYGDALA is a heterogeneous collection of nuclear groups located in the temporal lobe[1,2]. The various nuclei can be distinguished on the basis of cytoarchitectonics, chemoarchitectonics and fiber connections, and are collectively referred to as the amygdaloid complex[3,4]. A variety of different functions have been attributed to the amygdaloid complex, including memory, attention, interpretation of emotional significance of sensory stimuli, perception of body movements and generation of emotional aspects of dreams[5–19]. However, the amygdala's contribution to emotional processes, particularly to the detection of emotional events and the production of appropriate responses, is the most extensively investigated and best understood function of this part of the brain[20].

What sort of neuronal hardware might underlie the capacity of the amygdala to detect biologically significant events and orchestrate responses appropriate to the implied meaning of those events? In recent studies we have explored this question by examining patterns of information flow within the amygdala, as revealed by networks of anatomical connectivity between amygdala subregions. This has been done by making small injections of an anterograde tracer, *Phaseolus vulgaris*

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TABLE 1. Amygdaloid nuclei and nuclear divisions

Deep nuclei
Lateral nucleus (L)
- dorsolateral division (L_{dl})
- ventrolateral division (L_{vl})
- medial division (L_m)

Basal nucleus (B)
- magnocellular division (B_{mc})
- intermediate division (B_i)
- parvicellular division (B_{pc})

Accessory basal nucleus (AB)
- magnocellular division (AB_{mc})
- parvicellular division (AB_{pc})

Superficial nuclei
Nucleus of the lateral olfactory tract (NLOT)
Bed nucleus of the accessory olfactory tract (BAOT)
Anterior cortical nucleus (CO_a)
Medial nucleus (M)
- rostral division (M_r)
- central division
  - dorsal part (M_{cd})
  - ventral part (M_{cv})
- caudal division (M_c)

Periamygdaloid cortex
- periamygdaloid cortex (PAC)
- periamygdaloid cortex, medial division (PAC_m)
- periamygdaloid cortex, sulcal division (PAC_s)

Posterior cortical nucleus (CO_p)

Other amygdaloid areas
Anterior amygdaloid area (AAA)
Central nucleus (CE)
- capsular division (CE_c)
- lateral division (CE_l)
- intermediate division (CE_i)
- medial division (CE_m)

Amygdalo–hippocampal area (AHA)
- medial division (AHA_m)
- lateral division (AHA_l)

Intercalated nuclei (I)

leucoagglutinin (PHA-L), restricted only to one nuclear division of the rat amygdala. The findings have led to new understanding of how information is processed by the amygdala, and the purpose of this review is to describe the principles of intra-amygdaloid connectivity that have been uncovered in the rat.

Information flow

Information flow within the amygdala takes place via dense and precisely organized intradivisional and interdivisional pathways. We will consider three distinct levels of intra-amygdaloid connectivity: internuclear, interdivisional, and intradivisional. Internuclear connections are between two nuclei. Each nucleus, though, is made up of separate subdivisions which are connected via interdivisional pathways. Each subdivision, in turn, has its own intradivisional connections. On the basis of the findings to be described, we propose that the different nuclei and nuclear divisions (Table 1, Fig. 1) represent separate functional (computational) units, and that the processing of information within the amygdala involves highly organized patterns of communication within and between these (Figs 2 and 3).

Sensory information about the external world reaches the rat amygdala primarily by way of the lateral nucleus. This conclusion is based on studies which traced connections from sensory processing areas to the amygdala[3,21–24], recorded neural activity in the amygdala in response to sensory stimuli before and/or following association with emotional stimuli[25,26], and disrupted the acquisition of associations between neutral and aversive sensory stimuli by destroying the lateral nucleus[27,28]. These observations indicate the importance of understanding the nature of information processing in the lateral nucleus as a first step in the effort to understand intra-amygdala processing.

Lateral nucleus

Most of what we know about the sensory inputs to the lateral nucleus in the rat has come from studies of connections with the auditory system. Anatomical tracing studies suggest that input from the auditory thalamus terminate in the dorsolateral and ventrolateral areas, while input from cortical sensory areas terminate in all the divisions[21,29]. However, single unit recordings indicate that sensory information is mainly fed into the dorsolateral and ventrolateral divisions[25,29]. The latency of auditory evoked responses shows that the dorsolateral division receives the earliest information about auditory stimuli, presumably from the thalamus[25,29,30]. The dorsolateral division is also the amygdala site with the shortest latency conditioned responses elicited by sensory stimuli associated with aversive events in emotional learning tasks[26]. The fact that the dorsolateral region is a site of auditory and somatosensory convergence[29] may account for the enhancement of auditory evoked responses following the pairing of auditory and painful somatosensory stimuli[26]. The medial division, on the other hand, receives most of its input from higher order cortical processing regions, including the prefrontal and perirhinal cortical areas, and the hippocampal formation[29,31–33]. This may explain why it is largely unresponsive to sensory stimulation[25,29].

The lateral nucleus sends heavy projections to most of the other amygdaloid nuclei (Fig. 3). However, before information leaves the lateral nucleus it is likely to be subjected to a substantial degree of processing. The major connectivity rule is that the various divisions of the lateral nucleus do not initiate substantial intradivisional projections, but rather, each rostrocaudal level projects only a short distance (Fig. 2; A. Pitkänen and V. Savander,

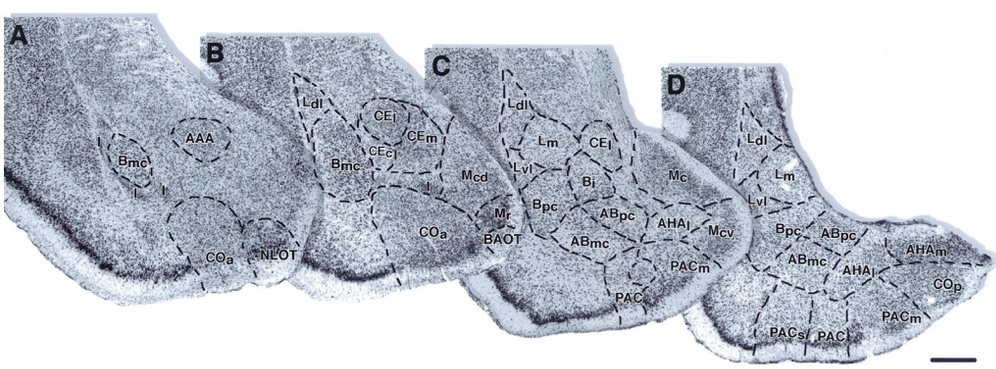

Fig. 1. ***The amygdaloid complex in the rat is composed of 13 regions, including specific nuclei and the periamygdaloid cortex.*** *Most of these regions have subdivisions, which suggests that the anatomical as well as the functional units of the amygdala are the nuclei and divisions. Panel A is most rostral and panel D most caudal. For abbreviations, see Table 1. Scale bar 0.5 mm.*

unpublished). Nevertheless, there are opportunities for local regulation of processing.

Although relatively little is known about local circuit organization in the amygdala, there is evidence that incoming signals are regulated locally by inhibitory interneurons in the dorsolateral division. For example, electrical stimulation of auditory processing areas in the thalamus results in the elicitation of a single spike followed by a period of inhibition lasting up to several hundred milliseconds in the dorsolateral division[34,35]. The first 30 ms of inhibition is mediated by $GABA_A$ receptors and the later aspects by $GABA_B$ receptors[35]. Evidence exists of both 'feedforward' and feedback inhibition in this pathway[35–37].

Each rostrocaudal level of the dorsolateral division gives rise to dense projections to the other two divisions of the lateral nucleus (see Fig. 1A). This allows information entering any part of the dorsolateral division to activate the other divisions. Information flow between these divisions is unidirectional, as the ventrolateral and medial divisions do not project back to the dorsolateral division. Further, interconnections between the ventrolateral and medial divisions are meager.

Basal nucleus

Unlike the lateral nucleus, the magnocellular, intermediate and parvicellular divisions of the basal nuclei have dense projections throughout their rostrocaudal extent (Fig. 2B). The only exception is the parvicellular division, in which the lateral and medial portions remain largely unconnected[38].

The interconnections of the three divisions of the basal nucleus are selective (Fig. 2B,C). The parvicellular division gives rise to most of the intranuclear projections within the basal nucleus and projects both to the magnocellular and intermediate divisions. Unlike the lateral nucleus, where there are no major reciprocal connections between the nuclear divisions, the magnocellular division of the basal nucleus sends a projection back to the lateral part of the parvicellular division. The intermediate division, however, does not give any substantial projections to the other divisions of the basal nucleus[38]. These observations suggest that in contrast to the lateral nucleus, each division of the basal nucleus is able to distribute the input throughout the division, and the magnocellular and parvicellular divisions may selectively activate the other divisions as well.

Considerably less is known about the physiology of the basal nucleus than the lateral nucleus from *in vivo* recordings, but there have been a number of *in vitro* studies of the basal nucleus[39–44]. Unfortunately, most of the physiological studies have not been done with the divisional distinctions in mind. It is thus not possible to discuss differences in the physiology of different parts of the basal nucleus.

Accessory basal nucleus

The two divisions of the accessory basal nucleus, the magnocellular and parvicellular, also give rise to dense intradivisional projections, but are connectionally separated from each other (Fig. 2D)[45]. Therefore, information arriving in one of the divisions is able to influence processes throughout most parts of that division but probably remains segregated from the content of the other division.

Central nucleus

The central nucleus is the major output nucleus for amygdaloid projections to the brainstem and hypothalamus. It is also one of the amygdaloid nuclei to receive input from both the lateral, basal and accessory basal nuclei. Interestingly, however, inputs from these three nuclei mostly terminate in different divisions of the central nucleus.

Each of the divisions of the central nucleus has heavy intradivisional projections along the rostrocaudal and mediolateral axes[46]. In addition, there is extensive interdivisional connectivity: capsular division projects

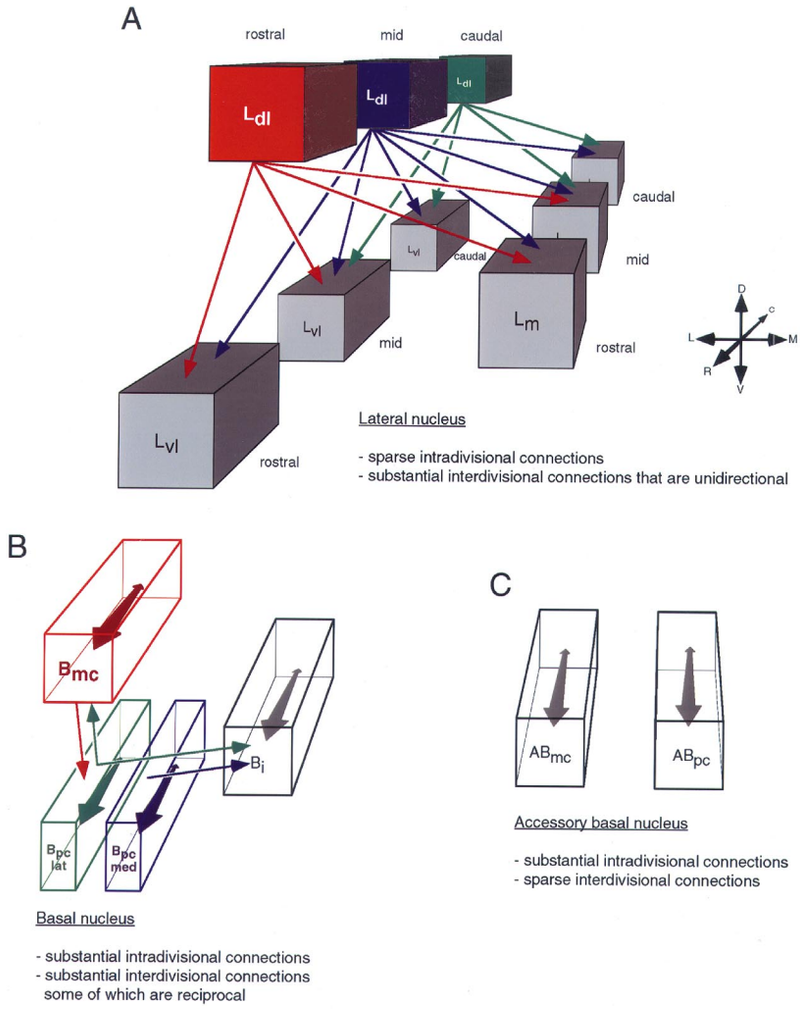

Fig. 2. ***Principles of intradivisional and interdivisional connectivity in the lateral, basal and accessory basal nuclei.*** **(A)** *In the lateral nucleus, the rostral, middle and caudal portions of various divisions (dorsolateral, ventrolateral, medial) do not project to other portions in a given division. Consequently, the information entering one portion of the division does not spread along the rostrocaudal extent of a division monosynaptically. The dorsolateral division projects to two other divisions of the lateral nucleus. However, the ventrolateral and medial divisions do not send any substantial projections to each other or to the dorsolateral division. Therefore, at the interdivisional level, the information flow in the lateral nucleus is largely unidirectional.* **(B)** *Unlike the lateral nucleus, each division of the basal nucleus has dense intradivisional projections throughout its rostrocaudal extent. Exceptions include the medial and lateral portions of the parvicellular division, which are not heavily interconnected. Most of the interdivisional connections originate in the parvicellular division. Importantly, the lateral and medial parts of the parvicellular division, which are connectionally separated from each other, project to the intermediate division of the basal nucleus, where the inputs converge. Unlike lateral nucleus, where there are no major reciprocal connections between the nuclear divisions, the magnocellular division of the basal nucleus sends a projection back to the lateral part of the parvicellular division.* **(C)** *In the accessory basal nucleus, the magnocellular and parvicellular divisions have substantial intradivisional projections. The projections between the divisions are meager, which suggests that one division remains independent of the information content entering the other division. Taken together, our observations suggest three major principles. First, intradivisional connections extend throughout the divisions of the amygdaloid nuclei, except in the lateral nucleus, where the intradivisional projections spread only to a narrow segment within a given division. Second, the various divisions in a given nucleus tend to be interconnected, but some exceptions exist. Third, interdivisional projections are typically unidirectional.*

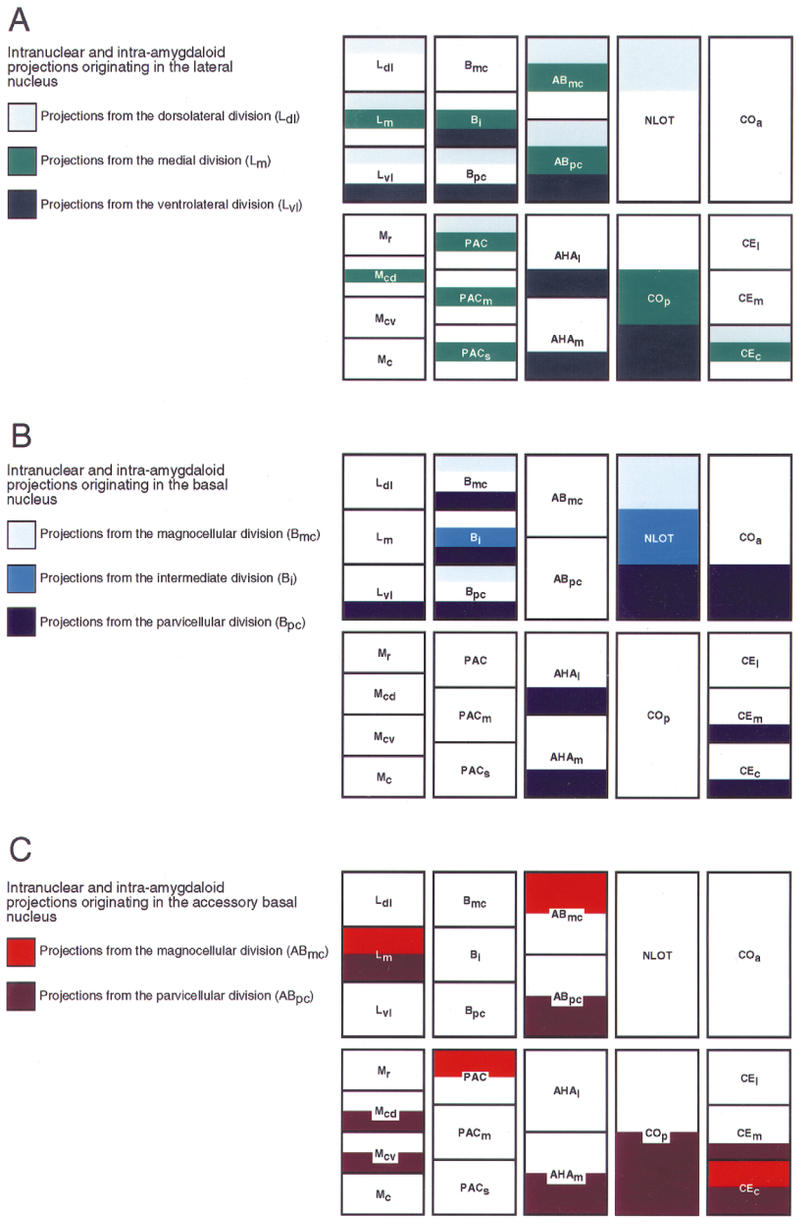

Fig. 3. ***Matrix of projections from the lateral (top), basal (middle) and accessory basal (bottom) nucleus to the other amygdaloid nuclei.*** *Projections originating in the different divisions of the lateral nucleus are indicated with different shades of green, those originating in the basal nucleus with different shades of blue, and in the accessory basal nucleus with different shades of red. In the data matrix on the right, each amygdaloid nucleus and nuclear division is shown as a separate box (for abbreviations, see Table 1). The color code within the box indicates where the input comes from. The data matrix suggests two major principles in the organization of the internuclear connections. First, each division of the lateral, basal or accessory basal nuclei projects at least to two other sites in the amygdala. As a consequence, the information entering any portion of the amygdala will have a representation in a selective set of other locations of the amygdala which receives inputs from other functional systems of the brain. For example, the representation of the sensory information from the ventrolateral division of the lateral nucleus will be delivered to the parvicellular and intermediate divisions of the basal nucleus, which receive input from the medial temporal lobe memory system; and to the parvicellular division of the accessory basal nucleus, which receives input from the hypothalamic network signaling the current state of an internal milieu. The second principle is that there is a significant amount of convergence of projections in the central nucleus and in the amygdalo–hippocampal area, which receive substantial input from all three nuclei.*

to the medial division; lateral division projects to the capsular and medial divisions; medial division projects back to the capsular division. The intermediate division is the only one that does not interact with the others. Therefore, the capsular and medial divisions are the major recipients of the inputs from the lateral, basal and accessory basal nuclei and are reciprocally interconnected. There remains a possibility that the most critical step of integration before the amygdala generates a behavioral response takes place in the interdivisional circuitries of the central nucleus.

Other nuclei

The different divisions of the medial nucleus are also interconnected[47]. However, the projections between the medial and lateral divisions of the amygdalo–hippocampal area are directed from lateral to medial direction[45,48].

Intra-amygdaloid projections

The intra-amygdaloid projections of various amygdaloid nuclei are mainly segregated, but converge in select amygdaloid regions. Projections from various cortical and subcortical areas to the amygdala terminate in different amygdaloid nuclei. For example, projections from sensory processing areas terminate in the lateral nucleus; projections from the entorhinal cortex terminate most heavily in the basal nucleus, but labeled terminals are also found in the central and lateral nuclei and peri-amygdaloid cortex; and projections from the hypothalamus terminate in the central, medial, basal and accessory basal nuclei[3,4]. These data suggest that the information entering the amygdala from various cortical and subcortical systems will have multiple, highly localized representations within the amygdala. How, then, does integration take place? For example, how is sensory information entering the amygdala in the lateral nucleus integrated with information coming to the amygdala from long-term storage systems involving the hippocampus and other components of the medial temporal lobe memory network, or with information about internal milieu from the hypothalamus? Obviously, intra-amygdaloid connections are responsible.

The lateral nucleus gives rise to the most extensive set of intra-amygdaloid connections (Fig. 2)[49]. However, the basal nucleus[38], accessory basal nucleus[45], periamygdaloid cortex[50], medial nucleus[47], anterior cortical nucleus[45] and posterior cortical nucleus[48] also have projections to the other amygdaloid nuclei. Each of these connections terminates only in select amygdaloid nuclei or nuclear divisions (Fig. 3). Even though this generates an extensive network of intra-amygdaloid connections, there is surprisingly little overlap between the terminal fields of projections originating in the different amygdaloid nuclei. The two regions where there seems to be a significant amount of convergence of projections are the central nucleus and the amygdalo–hippocampal area (Figs 3,4).

The connectional organization of the amygdaloid nuclei suggests several conclusions. First, after entering the amygdala, a stimulus will soon have several representations that are processed in parallel. Second, after association of information from the other functional systems of the brain, each of the nuclei or nuclear divisions comes to have a unique representation of the stimulus qualities. This might indicate that each nucleus or nuclear division processes different components of a given task or carries out different function(s). Third, the overlap of the projections in select amygdaloid nuclei might be important, for example, for the association and fine tuning of information processed in parallel within the amygdaloid networks.

The fact that the lateral, basal and accessory basal nuclei send converging projections to two output regions

of the amygdala, the central nucleus and the amygdalo–hippocampal area, may provide an anatomical basis for understanding how both external and internal stimuli can induce similar behavioral responses in spite of the fact that they enter the amygdala via different nuclei. Such a mechanism might be valuable, for example, in life-threatening situations, where similar behavioral actions are to be executed regardless of the modality or nucleus through which the hazardous signal reaches the amygdala. Such organization of intra-amygdaloid connections may also explain, for example, how the behavioral responses in various anxiety disorders may be stereotypical even though the stimuli that evoke them differ remarkably between disorders and between individuals.

Reciprocal information flow

The information flow within the amygdaloid complex is reciprocal rather than unidirectional. Previously it was widely accepted that the information flow within the amygdala was strictly unidirectional, that is, from lateral to medial areas[3,4,51]. According to this hypothesis, only a few projections, if any, reciprocate back to the lateral nucleus. However, as we and other authors have demonstrated, this is not the case (Fig. 5). For example, virtually all main intra-amygdaloid targets of the lateral nucleus, with the possible exceptions of the central nucleus and the amygdalo–hippocampal area, send projections back to the lateral nucleus. The basal nucleus appears to send morphologically defined inhibitory and excitatory projections to the ventrolateral division of the lateral nucleus[52]. The inhibitory component of this projection has also been demonstrated electrophysiologically *in vitro* by stimulating or applying glutamate to the basal nucleus and recording hyperpolarizing GABA receptor mediated responses from the lateral nucleus[53]. The accessory basal nucleus sends a morphologically defined excitatory projection to the medial division of the lateral nucleus[52]. Moreover, the PAC division of the periamygdaloid cortex projects the lateral nucleus to the ventrolateral and medial divisions[50]. In addition, the anterodorsal part of the medial nucleus sends projections back to the ventrolateral and medial divisions of the lateral nucleus[47]. The reciprocal connections are of substantial density even though they typically tend to be lighter than their input projections from the lateral nucleus. Via these reciprocal connections the intra-amygdaloid target areas of the lateral nucleus could control their own inputs from the lateral nucleus. On the other hand, these connections might constitute routes through which extra-amygdaloid regions providing afferents to these areas can influence the early stages of amygdaloid processing of sensory information at the level of the lateral nucleus, that is, they might set the 'strength of the filter' within the lateral nucleus. For example, hunger might affect how easily the visual impulses reaching the lateral nucleus from food items will have access to the intra-amygdaloid circuitries and elicit a motor response. Also the basal nucleus and the accessory basal nucleus are reciprocally connected with their target regions, such as the anterior cortical nucleus or the medial and posterior cortical nuclei, respectively[47,48].

The organization of the intra-amygdaloid connections of the central nucleus and the amygdalo–hippocampal area, however, is different from the other amygdaloid nuclei. Even though they receive substantial projections from the lateral, basal and accessory basal nuclei, they send very meager projections back to these amygdaloid areas. Moreover, these nuclei have very light interconnections (Jolkkonen and Pitkänen, unpublished; Refs 45,48). These data suggest that the major function of these nuclei is to execute output commands rather than modulate incoming information.

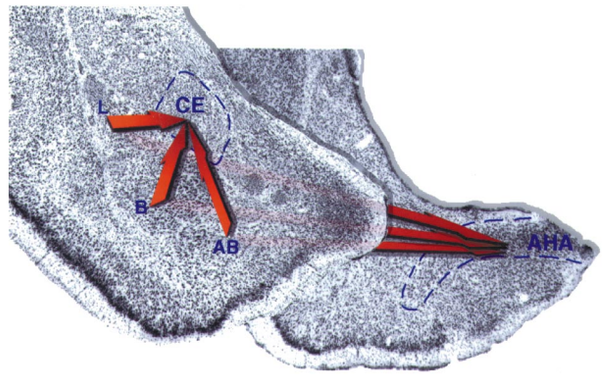

Fig. 4. ***Inputs from different amygdaloid nuclei converge in the central nucleus and in the amygdalo–hippocampal area.*** *For example, the capsular division of the central nucleus receives input from the dorsolateral and medial divisions of the lateral nucleus, from the parvicellular division of the basal nucleus and from both the magnocellular and parvicellular divisions of the accessory basal nucleus. The medial division of the amygdalo–hippocampal area, in turn, is a target for the ventrolateral division of the lateral nucleus, the parvicellular division of the basal nucleus and the parvicellular division of the accessory basal nucleus. This convergence of input suggests that various kinds of stimuli may elicit relatively stereotypical behavior independent of their entry region to the amygdala, because all major input nuclei project to the final output stations.*

Extrapolation of the data on rodents to primates

Recent PHA-L studies show the three levels of topographically organized intra-amygdaloid connections (intradivisional, interdivisional and internuclear) are also

Fig. 5. ***The information flow within the amygdala is not unidirectional but reciprocal.*** *For example, the lateral nucleus is the major input nucleus for the sensory information entering the amygdala and is reciprocally connected with its main projection nuclei. Interestingly, however, the central nucleus and the amygdalo–hippocampal area, which receive convergent information from several amygdaloid nuclei, do not project back to their input regions in the lateral, basal or accessory basal nuclei.*

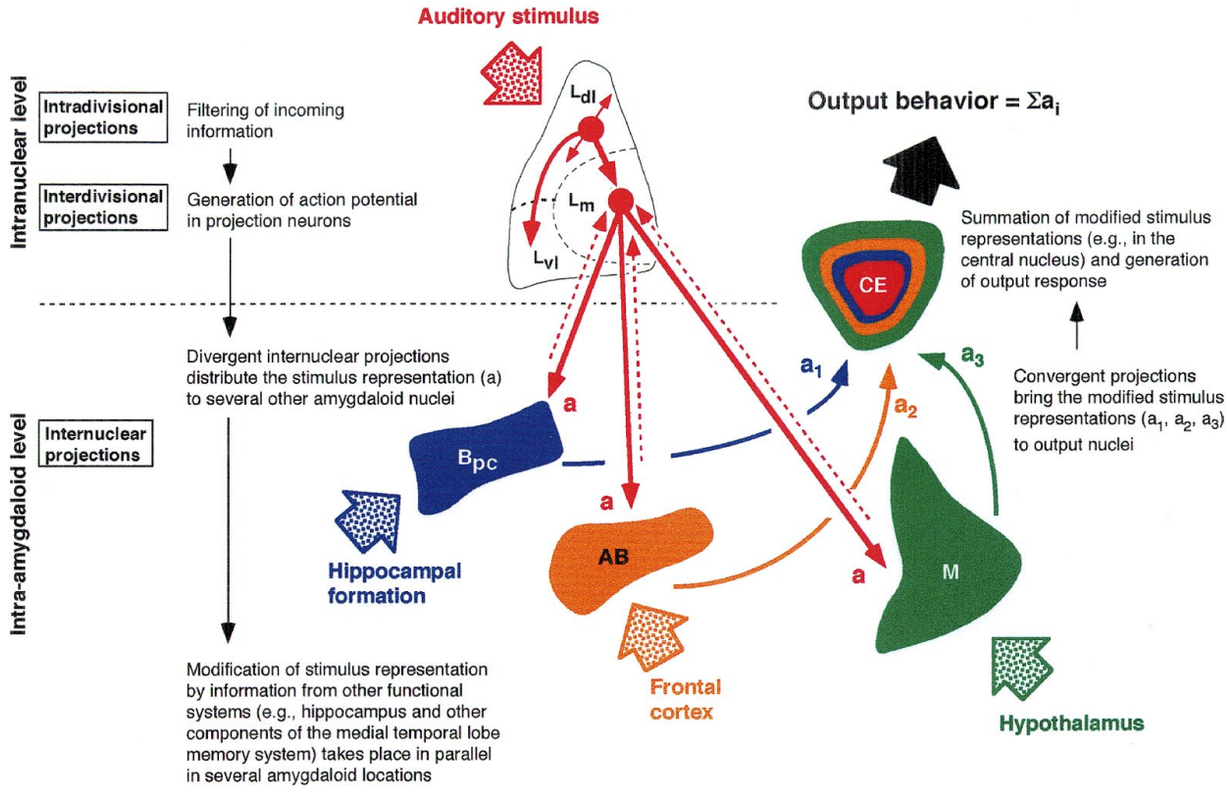

Fig. 6. ***The three levels of intra-amygdaloid connectivity: intradivisional, interdivisional and internuclear.*** *When signals enter the amygdaloid complex they become subject to the intradivisional (that is, within the dorsolateral division of the lateral nucleus) and interdivisional (that is, between the dorsolateral division and the medial division of the lateral nucleus) processing which probably determines whether the signal will be distributed to the other amygdaloid nuclei via internuclear connections (that is, from the lateral nucleus to the basal nucleus). If the intra-amygdaloid projection neurons in a given nucleus elicit action potentials, the signal will have several representations (for example, information initially represented in the medial division of the lateral nucleus might become distributed to the parvicellular division of the basal nucleus, accessory basal nucleus and medial nucleus); and it will be modulated in parallel in several amygdaloid locations (for example, in the parvicellular division of the basal nucleus the signal could become associated with the information from the medial temporal lobe memory system; in the accessory basal nucleus it could become integrated with information about the internal milieu by connections from the hypothalamus). Because the projections from many amygdaloid nuclei converge in selective amygdaloid output regions (for example, in the central nucleus), the behavioral response might be a sum of the modulated signal representations.*

present in the monkey amygdala, at least in the lateral nucleus[54]. The evidence supporting the existence of reciprocal connectivity in primates is weak at the moment (for review, see Ref. 4). For example, the accessory basal nucleus might project lightly to the basal and lateral nuclei. However, these data were based on studies where tritiated amino acids were used as a tracer substance and, therefore, must be confirmed by more discrete tracer methods. However, as in rat, the central nucleus and the amygdalo–hippocampal area receive converging projections from the lateral, basal accessory, basal, medial and central nuclei in the monkey[4]. Based on the data available, it seems fair to conclude that the connectional organization of the monkey amygdala is similar to rather than different from that of the rat.

Nevertheless, the basic question of how the anatomical differences, such as the enlarged relative size of the lateral nucleus in primates compared to rats, translates to behavior, remains to be revealed in future studies.

Conclusions

The hierarchial organization of the intra-amygdaloid connections suggests several principles that may take place after information enters the amygdaloid complex (Fig. 6). At the site of input, local filtering mechanisms within the intradivisional circuitries might determine whether incoming neuronal activity will evoke a response. If a response is evoked, neuronal activity spreads within the division or becomes distributed to the other divisions or to the other amygdaloid nuclei in point-to-point manner. As a consequence, representations of the input information are established in parallel in different locations of the amygdaloid complex, with each location receiving input from other selective areas of the brain. After information becomes associated with or modulated by information from the other functional systems processed in parallel in different locations of the amygdala, it enters the output regions of the amygdala, particularly the central nucleus and the amygdalo–hippocampal area. The convergence of inputs in these areas might serve to gather the modulated stimulus representations and to bring them together finally to elicit appropriate behavioral responses.

It is no longer appropriate to view the amygdala as a complex, poorly understood region of the brain with little systematic organization. Studies of internal circuitries show that the amygdala has a clear and precise organization that is tailored to the computational functions it performs.

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GABA$_A$, NMDA and AMPA receptors: a developmentally regulated 'ménage à trois'

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The main ionotropic receptors (GABA$_A$, NMDA and AMPA) display a sequential participation in neuronal excitation in the neonatal hippocampus. GABA, the principal inhibitory transmitter in the adult CNS, acts as an excitatory transmitter in early postnatal stage. Glutamatergic synaptic transmission is first purely NMDA-receptor based and lacks functional AMPA receptors. Therefore, initially glutamatergic synapses are 'silent' at resting membrane potential, NMDA channels being blocked by Mg^{2+}. However, when GABA and glutamatergic synapses are coactivated during the physiological patterns of activity, GABA$_A$ receptors can facilitate the activation of NMDA receptors, playing the role conferred to AMPA receptors later on in development. Determining the mechanisms underlying the development of this 'ménage à trois' will shed light not only on the wide range of trophic roles of glutamate and GABA in the developing brain, but also on the significance of the transition from neonatal to adult forms of plasticity.

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THE DEVELOPMENT AND FORMATION of neuronal circuits is a relatively rapid sequence of events during which neurones migrate, arborize and establish synaptic connections, some of which are stabilized and others eliminated. Neuronal activity appears to play a crucial role in coordinating this formation: 'neurones that fire together wire together'[1–3]. As in adult forms of synaptic plasticity, this modulation is mediated largely by increases in the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) that activate a wide range of intracellular cascades. Studies on the ontogeny of membrane properties of excitable cells have revealed a

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