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The dopaminergic projection system, basal forebrain macrosystems, and conditioned stimuli

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Abstract

This review begins with a description of some problems that in recent years have beset an influential circuit model of fear-conditioning and goes on to look at neuroanatomy that might subserve conditioning viewed in a broader perspective, including not only fear, but also appetitive, conditioning. The paper then focuses on basal forebrain functional-anatomical systems, or macrosystems, as they have come to be called, which Lennart Heimer and colleagues described beginning in the 1970's. Yet more specific attention is then given to the relationships of the dorsal and ventral striatopallidal systems and extended amygdala with the dopaminergic mesotelencephalic projection systems, culminating with the hypothesis that all macrosystems contribute to behavioral conditioning.

There is tremendous current interest in the neurobiological mechanisms underlying conditioned fear stemming in large part from an increasing prevalence in American culture of anxiety and panic disorders, not to mention PTSD[1]. By 2000, the relevant brain circuitry had seemed to be satisfactorily described[2], but a number of serious caveats had been voiced the preceding year[3], and an unraveling process accelerated thereafter. Indeed, current theory on the neural substrates of fear conditioning has entered into a state of reassessment[4].

The essential elements of fear conditioning are described by the observation that pairing neutral and fear-arousing stimuli causes the neutral one to gain meaning such that it can then drive an organism's voluntary and involuntary actions. Thus, behaviorally, rats exposed to a brief tone followed immediately by a footshock will soon, frequently after a single trial, come to "freeze" upon hearing the tone. In LeDoux's[2] model of this phenomenon, neuroplasticity reflecting the attachment of "significance" to a neutral stimulus, i.e., heralding the transformation of neutral to conditioned stimulus (CS), occurs in the amygdala, specifically its lateral nucleus (LA). According to LeDoux's model, LA projects to another part of the amygdala, the central nucleus (CeA), which, in turn sends out divergent descending projections to somatic and autonomic motor effectors in the brainstem, eliciting behavioral freezing and accompanying autonomic responses. Consistent with the model, [1] sensory inputs bearing information about the aversive and neutral (to be conditioned) stimuli converge in LA[5], and [2] an increase in the efficacy of CS-related synapses corresponds to conditioning[6–8]. But, soon it was realized that the CeA consists of two parts, a medial division (CeAm) from which most of its descending projections arise and to which LA does not project, and a lateral one (CeAl) to which it does. While CeAl projects to CeAm and thus might serve as a relay interposed between LA and CeAm, the CeAl to CeAm projection is nearly exclusively inhibitiory (GABAergic) and thus would inhibit rather than activate outputs to brainstem. The model was accordingly adjusted to emphasize instead a projection from LA to amygdaloid "intercalated" nuclei[9], which are

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located between CeAm and CeAl and project to CeAm. This also is a GABAergic projection, however, making it is difficult to conceive how this solves the problem, but because intercalated nuclei comprise several interconnected cell masses, it was reasoned that activation of one would inhibit its neighbor, which in turn would disinhibit the CeAm[10]. This seems a possible, but precarious, foundation upon which to build such a biologically important function as fear conditioning, and, in any event, more issues came to plague the model (e.g., Ref. 11) Despite this accumulation of complications, the status of the amygdala as a major player in stimulus-consequence associations[12–15], seems not to be in jeaopardy (e.g., Refs. 4 and 16), although the underlying brain circuitry and physiological mechanisms appear to require further investigation.

In considering this dilemma, recall that conditioning occurs not only in response to fear-arousing and aversive stimuli, but also to appetitive cues, as in, e.g., conditioned place preference (e.g., Refs. 17 and 18) and postural orienting directed to a CS (e.g., Refs. 19 and 20), and not only in the amygdala. Indeed, appetitive Pavlovian conditioned responses are abolished by lesions in the accumbens territory of the ventral striaum[17], which turns out to also contribute to specific forms of aversive conditioning[21–24]. Moreover, lesions of the CeA not only abolish aversive conditioning, as in freezing to a CS, as described above, but also disrupt orienting to appetitive conditioned cues[16, 25]. Thus, both structures support Pavlovian responses to fear-arousing and appetitive stimuli, although each may “specialize” in one or the other. This suggests that both structures possess a general capacity to recognize stimulus “significance” and a more specialized capacity to assess the associated adaptive implications in order that a proper Pavlovian response will be mounted. Insofar as function follows structure, it seems reasonable to expect that the neuroanatomical organizations of the CeA and accumbens also should exhibit both similarities and differences and that these might provide some additional insight into the neural mechanisms that underlie conditioning.

This expectation is fulfilled by the concept of basal forebrain functional-anatomical systems or macrosystems, as they came to be called[26, 27]. Among these, are the dorsal striatopallidal system (basal ganglia as classically described), ventral striatopallidal system (which, relevant to this discussion, includes the accumbens[28, 29]) and extended amygdala (which includes the CeA[30]). Structural similarities shared by different macrosystems are reflected in a basic “framework”, essentially that of the basal ganglia[30], in which massive projections from the cortical mantle or cortical-like structures[31–33], a category that includes LA, terminate densely in subcortical “input” structures consisting predominantly of medium-sized, densely spiny inhibitory (i.e., GABAergic) neurons. Macrosystem input structures, including the CeA and accumbens, also receive massive inputs from the brainstem reticular formation via the midline/intralaminar thalamic nuclei and brainstem monoaminergic cell groups, especially dopaminergic. Medium spiny neurons, in turn, may project out of the macrosystem, as outputs, or massively to structures regarded as part of the macrosystem “intrinsic” circuitry constituting somewhat larger sparsely-spined, GABAergic “pallidal”-like neurons with long radiating aspiny dendrites, such as found in the globus pallidus, ventral pallidum and CeAm. Pallidal-like neurons also may project intrinsically or give rise to outputs. Macrosystem outputs diverge into [1] reentrant pathways to the forebrain, including cortex, via synaptic relays in the thalamus, forebrain and brainstem and [2] descending pathways to somatic and autonomic motor effectors, via relays in the hypothalamus, mesopontine tegmentum and caudal brainstem. Accompanying the host of basic similarities shared by macrosystems are a variety of features that distinguish them, such as the richness and extent of medium spiny neuronal intrinsic axonal arbors, the numbers and transmitter phenotypes of associated large interneurons and the quantity and indentities of neuropeptides, neuropeptide and transmitter receptors, and intracellular signaling cascades utilized[30, 34–36].

This paper takes a closer look at the dopaminergic innervation of macrosystems. Early pioneering studies revealed with astounding clarity that catecholaminergic and indoleaminergic cell groups embedded in the brainstem provide ascending and descending projections to virtually all parts of the brain and, particularly abundantly, to the basal ganglia and other basal forebrain structures[37–41]. By distinguishing different fluorescent hues, these investigators discriminated norepinephrine and dopamine (which emit at similar wavelengths and were designated as "A" cell groups and projections) from serotonin (B groups) and epinephrine (C groups). Among the catecholamine-fluorescing cell groups subsequently identified as dopaminergic[42], the A8, A9 and A10 groups, occupying, respectively, the midbrain retrorubral field, substantia nigra compacta (SNc) and ventral tegmental area (VTA), are related by connections most strongly to the basal forebrain macrosystems. Although individually designated, A8, A9 and A10 actually comprise a single continuous constellation of dopaminergic neurons (Fig. 1A–F), approximating the form of an ellipsoid encircling the medial lemniscus with A10 (occupying the VTA) lodged in the ventromedial tegmentum and A8 (occupying the retrorubral field) and A9 (occupying the SNc), respectively, extending lateralward above and below the medial lemniscus to meet again in the ventrolateral tegmentum. In addition, an appendage of A8 arches caudomedialward toward the ventrolateral periaqueductal gray (Fig. 1F). Where confluent (e.g., * in Fig. 1A and ** in Fig. 1B), neurons in A8 are indistinguishable from those in A9 or A10, as are those in A9 from those in A10. Nonetheless, A8, A9 and A10 are structurally and functionally differentiated, as is reflected in the relatively distinct, albeit overlapping, topographies of their ascending projections[43–50], to be discussed below. Hökfelt et al.[51] designated some additional dopaminergic districts, of which only one will be mentioned here - A10dc (dc - dorsal, caudal) is located in the mesopontine periaqueductal gray (PAG) in the vicinity of the dorsal raphe nucleus (Figs. 1F and 2B).

A9 (the SNc) gives rise to the *mesostriatal* projection, which, essentially, provides dense dopaminergic innervation to the caudate nucleus and putamen (i.e., the "input" nuclei of the basal ganglia). The caudate-putamen, which also receives massive input from isocortex (neocortex), is involved in the initiation and control of voluntary movements, development and maintenance of motor habits, and possibly the structuring of some cognitive processes[52]. In turn, the caudate-putamen and other basal ganglia structures, including the globus pallidus and substantia nigra project prominently to A9, which also receives ascending afferents from a number of structures in the brainstem. *Mesolimbic* projections, from A10 (in the VTA), provide a dense dopaminergic innervation to ventral striatopallidum, and, to a lesser extent, the extended amygdala (CeA, bed nucleus of stria terminalis and associated structures), as well as to a number of other sites in the basal forebrain, such as the septum and preoptic region. All of these structures project back to A10 directly, but this forms but part of the A10 afferent system, which comprises a nearly continuous and extensively interconnected formation of structures extending from the prefrontal cortex to the caudal brainstem[53–56]. Mesolimbic dopaminergic projections are reported to be involved in a broad range of functions, including locomotor activation (e.g., Ref. 57), reward (e.g., Ref. 58), motivation (e.g., Ref. 59), novelty detection (e.g., Ref. 60), reward prediction and error detection (eg., Ref. 61), and memory and learning (e.g., Ref. 62). Moreover, A10 and its projections, particularly to the accumbens, were identified early on as the primary sites of attack of psychostimulant and opiate drugs of abuse, which were said to "hijack" the reward system. The A10 dopamine-accumbens axis soon became regarded as the target most subject to maladaptative neurochemical, molecular and electrophysiological reorganizations in response to chronic (and acute, as it turns out) administration of such drugs (e.g, Refs. 63 and 64).

In contrast, A8 (the retrorubral field) and its projection system and neural connections, by comparison, have been relatively neglected, having not even been considered in one classic

description of the ventral mesencephalic efferents[65]. Nor did Lindvall and Björkland[46] or Fallon and Loughlin[47, 48] have much to say about A8 in their respective chapters on central dopamine-containing neuronal systems, and Fallon[50] intentionally omitted consideration of A8 in deference to a brief report on it in the same congress[49]. As it turns out, just as A9 is most closely associated with neostriatum and the somatomotor apparatus, and A10 with the ventral striatopallidum[36], A8 appears to be closely related to extended amygdala, which, as noted above, a substantial literature ties closely to behaviors driven by fear and anxiety (see also Refs. 66–68). The paper by Deutch et al.[49] sketched out connections of A8 with structures that would in the same year be defined as comprising the central division of the extended amygdala[30] and subsequent tract tracing studies have born out this connectional relationship. Thus, A8 is densely innervated by the central nucleus of the amygdala[69, 70] and bed nucleus of stria terminalis[36, 71]. Interestingly, fibers descending from extended amygdaloid structures mainly pass through the VTA (A10) with minimal functional relationship (few axonal varicosities, regarded as sites of synaptic potency) before turning lateralward toward A8 and the lateral part of A9 (Figs. 1A–F and 2A), where many terminal axonal branches and axonal varicosities are observed. This varicosity-rich descending projection of the extended amygdala then continues beyond A8 to enter the periaqueductal gray, where it forms another dense plexus of varicosity-laden terminations among the putatively dopaminergic neurons comprising Hökfelt et al.'s[51] A10dc (Figs. 1F and 2B). It has recently been shown that A10dc, which may utilize L-DOPA as a neurotransmitter in place of dopamine[52], represents that part of the A8–A10 complex that projects most robustly to the central division of the extended amgydala[73], followed in decreasing order by A10 proper, A8, and A9 (Table 1). Thus, it may make sense to group A10dc neurons with A8, in view of their rich connectional relationship with the extended amygdala.

To summarize, fear conditioning is inadequately addressed by a circuit model proposed by Ledoux and colleagues. Conditioned stimuli reflecting fear-arousing and appetitive associations, are best subserved by the amygdala and accumbens, respectively, although the amygdala can modulate the formation of certain forms appetitive, as can the accumbens the formation of certain forms of aversive, associations. In view of this evidence one might hypothesize that the capacity to recognize that a stimulus is significant, a more general aspect of Pavlovian conditioning, is reflected in neuroanatomical organization common to macrosystems, whereas synthesizing an appropriate response to specific stimulus modality, i.e., fear-arousing or appetitive, is reflected in their unique neuroanatomical features. Put more succinctly, the capacity of brain to form neural associations reflecting the interrelationships of various internal and external stimuli is hypothesized to be a property of all basal forebrain macrosystems and to involve their intrinsic and extrinsic connections.

It has been shown herein that shared and unique features also the characterize the dopaminergic connections of macrosystems. Consistent with the striking reciprocity of connections between the SNc (A9) and caudate-putamen, VTA (A10) and accumbens, and A8/A10dc and extended amygdala, lesions and perturbations of dopaminergic innervations in the extended amygdala and accumbens do disrupt fear and appetitive conditioning, respectively[74–79] and opposing modulations of the activity of dopaminergic neurons have been correlated with the presentation and omission of appetitive stimuli[61]. While the precise role played by dopaminergic mechanisms within the macrosystems in the formation and expression of associations underlying conditioning remains to be determined, it seems likely that such associations are an important element in most of the functions that have been attributed to dopamine, such as locomotor activation, reward, motivation, novelty detection, reward prediction, error detection and memory and learning (refs. cited above). The likelihood that dopaminergic actions on association formation play out in several different basal forebrain macrosystems, including the dorsal and ventral striatopallidum, extended amygdala, and the septal-preoptic system[30, 33, 36, 80], all acting somewhat differently on the

same and different sets of neural associations, suggests that the use of dopaminergic drugs, whether therapeutic or illicit, may have wide ranging behavioral effects.

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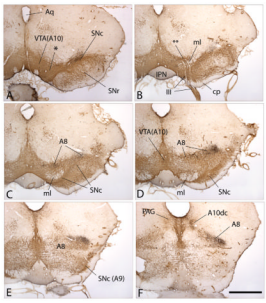

Figure 1.

Figure 1A–F. Photomicrographs illustrating a series of sections through the mesencephalon of the rat shown from A to F in rostrocaudal order. The sections were processed to exhibit immunoreactivity against tyrosine hydroxylase, which marks ventral mesencephalic dopaminergic neurons and axons brown, and thus shows the ventral tegmental area (VTA(A10)), substantial nigra pars compacta (SNc(A9)), and retrorubral field (A8). The juncture of VTA(A10) and SNc(A9) is indicated by * in panel A, as is the zone where VTA(A10) becomes A8 by ** in panel B and continuities between A10, A9 and A8 can be observed in all of the panels. Note in panel A that the dendrites of SNc(A9) dopaminergic neurons extend downward into the substantia nigra pars reticulata (SNr). Panel F illustrates the caudomedial extension of A8 and the tyrosine hydroxylase-immunoreactive (possibly L-DOPA containing) neurons in the periaqueductal gray (PAG), which are designated as A10dc. The black substance in all of the panels marks axons projecting from the central extended amygdala, specifically from the bed nucleus of stria terminalis, that were labeled in the laboratory with a dye. Note that the labeled pathway skirts past the SNc in panels A and B to terminate relatively exclusively within A8. The labeled axons in A8 and A10dc shown panel F are enlarged in Figs. 2A and B, respectively. Other abbreviations: III - oculomotor (3rd cranial) nerve and roots; Aq - cerebral aqueduct; cp - cerebral peduncle; IPN - interpeduncular nucleus; ml - medial lemniscus. Scale bar: 1 mm.

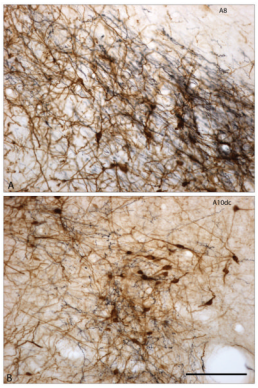

Figure 2.

Figure 2A and B. Photomicrographs showing enlargements of areas designated as A8 and A10dc in Fig. 1F. Tyrosine hydroxylase immunoreactive elements are brown and dye-labeled axons projecting from the bed nucleus of stria terminalis are black. The dye-labeled axons form a dense plexus of fibers containing many varicosities suggestive of abundant synaptic contacts. Scale bar: 100 μm.

Table 1

Numbers and % total of tyrosine hydroxylase immunoreactive neurons innervating the central nucleus of the amgydala (CeA) and bed nucleus of stria terminalis (BST)*

Dahlström and Fuxe (1964) designation	Conventional nomenclature	CeA	% total	BST	% total
A10dc**	periaqueductal gray	490	45.3	574	42.9
A10	ventral tegmental area	259	24.0	324	24.2
A8	retrorubral field	130	12.1	153	11.4
A9	substantia nigra compacta	97.0	9.0	44.0	3.3
A12	hypothalamic arcuate nucleus	39.7	3.7	122	9.1
A11	periventricular gray	28.3	2.6	29.5	2.2
A14	periventricular hypothalamus	27.1	2.5	82.0	6.1
A13	medial zona incerta	8.4	0.8	9.5	0.7

* Data were re-calculated from Table 1 in Hasue and Shammah-Lagnado (2002) and reflect the average numbers (CeA [n=7]; BST [n=2]) and percentages (% total) of retrogradely labeled perikarya that were tyrosine-hydroxylase immunoreactive. Perikaryal profiles were counted in every section of a 160 μm-spaced series.

** Structures are listed in order of descending % total. A10dc designation is from Hökfelt et al. (1984)