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Multidimensional processing in the amygdala

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Abstract

Brain-wide circuits that coordinate affective and social behaviours intersect in the amygdala. Consequently, amygdala lesions cause a heterogeneous array of social and non-social deficits. Social behaviours are not localized to subdivisions of the amygdala even though the inputs and outputs that carry social signals are anatomically restricted to distinct subnuclear regions. This observation may be explained by the multidimensional response properties of the component neurons. Indeed, the multitudes of circuits that converge in the amygdala enlist the same subset of neurons into different ensembles that combine social and non-social elements into high-dimensional representations. These representations may enable flexible, context-dependent social decisions. As such, multidimensional processing may operate in parallel with subcircuits of genetically identical neurons that serve specialized and functionally dissociable functions. When combined, the activity of specialized circuits may grant specificity to social behaviours, whereas multidimensional processing facilitates the flexibility and nuance needed for complex social behaviour.

Survival often depends on the individual's ability to integrate into a social group. Social behaviour is coordinated by a distributed network of brain areas that include the amygdala, an ancient structure that is already present in reptiles[1] and known to be a central hub for processing affective stimuli in many mammalian species. Compared with its role in assigning value (or valence) to environmental stimuli, the social functions of the amygdala are less well understood. Social deficits caused by temporal lobe lesions that included the amygdala were first reported more than a century ago[2]. However, the specific contribution of the amygdala to social behaviour is still debated, as a series of lesion studies, based on increasingly refined techniques, failed to converge on a core function for this structure. Instead, amygdala lesions produced a full list of social deficits, including faulty face and gaze processing and changes in aggression, submission, trust or social status, which in combination result in context-inappropriate social behaviours and disadvantageous social judgements (TABLE 1; also see REF.[3]). These deficits were often entangled with abnormalities in attention, arousal, defensive behaviours, salience or relevance detection and value-based decision-making (for example, see REFS[4,5]).

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Cell type-specific circuit manipulations in the rodent amygdala have in the past 5 years identified clusters of neurons that, when activated or inactivated, produce or prevent select behaviours[6]. The shared genetic identity and connectivity of these neurons determines the role they play in diverse processes such as valence assignment[7–9] or feeding[10,11]. Even more complex behaviours, such as prey pursuit and prey capture, have been shown to depend on subdivisions of the central nucleus of the amygdala (CeA), with each behaviour assigned to distinct clusters of neurons that project to different targets in the brainstem[12].

In contrast to this mosaic of specializations in amygdala circuits is the observation that neurons in the amygdala have multidimensional response properties[13]. Indeed, when monitored during tasks that require the activation of multiple functions of the amygdala, each amygdalar neuron responds to multiple types of stimuli and multiple, often disparate, task parameters[14–17]. These and other similar observations suggest the presence of an organizational scheme in the amygdala in which individual neurons hold membership in multiple, functionally distinct, neural ensembles. The resulting multidimensional representations[18,19] permit flexible strategies to navigate the complex, ever-changing social environment. In a broader perspective, multidimensional processing is not unique to the amygdala or to the social domain, but the amygdala illustrates this neurophysiological feature, which is shared with high-level associative cortices, particularly well.

In this Perspective, I aim to contrast established ideas of neural specializations with new concepts of multidimensional processing and to discuss from this viewpoint the foundation of social specializations in the primate amygdala. The emphasis on social behaviour is justified by the unusually large contribution of social factors to affective states coordinated by the amygdala. The emerging view is that multidimensional processing and functional compartmentalization are difficult to reconcile in the framework of simple psychological constructs such as attention, perception, valence or salience detection. In a higher-dimensional and more abstract framework, however, these two alternatives can be reconciled.

The amygdala in social behaviour

Is the amygdala necessary for normal social behaviour?

In order to establish the necessity of the amygdala for social behaviour, this section focuses on lesions and causal manipulations of the entire amygdala; however, studies addressing nucleus-specific lesions or pharmacological manipulation of the amygdala are also mentioned. The rich literature of neuroimaging and electrophysiological studies that implicate the amygdala in social behaviour has been reviewed elsewhere[20,21].

The amygdala acquired its place in the inventory of brain areas necessary for social behaviour from the earliest descriptions of deficits that are caused by removal of the temporal lobes, including the amygdala[2]. One of the earlier lesion-based research studies claimed that the amygdala is necessary for survival[22]. In this study, adult vervet monkeys with bilateral amygdala lesions were returned after amygdalectomy to their social group to continue living in their natural environment. These monkeys showed no interest in others, did not behave according to their pre-surgical social status, ignored or failed to understand

the signals of their peers, became isolated, defenceless and anorexic, and died in a few weeks. In later studies, as the amygdala lesions became more selective and the testing environments less naturalistic, the number and severity of the deficits in social behaviour shrank to approximately a dozen key features (TABLE 1). Only limited consensus can be extracted from the literature on amygdala lesions; the extent and developmental timing of the lesion, the socialization of the subjects preceding and following the lesion, and the tests used to quantify the social deficits have generated divergent and often contradictory outcomes[23].

Nevertheless, a few reliable threads weave through the fabric of these observations. Bilateral destruction of the amygdala in adult male monkeys often causes a fall in social status and the erasure or reduction of their natural wariness of others, and may increase or reduce aggression as well as affiliative or submissive behaviours (TABLE 1). When engaged by social partners, animals that have undergone amygdalectomy can respond to social cues and produce meaningful social behaviours, but their responses are typically context-inappropriate. By contrast, neonatal lesions in the amygdala leave more subtle sequelae or none at all, suggesting that the amygdala is not required for social behaviour and that its absence can be compensated for by redundant circuits and neural degeneracy. For example, the amygdala and the anterior cingulate cortex both contribute to the perception, and perhaps even the production, of facial expressions[24].

The literature on lesions suggests that the amygdala may not be strictly necessary for any aspect of social behaviour but, given its extensive connectivity, it is probably necessary to fine-tune and add nuance to social behaviour and co-opt non-social functions (such as value processing) to support social decisions. Indeed, functional imaging and neural recordings in both humans and non-human primates strongly support this view. According to these correlative studies, the amygdala plays a role in: social decision-making[20]; observational learning and vicarious reward processing (reviewed elsewhere[25]); face, gaze and eye-contact processing (reviewed in REF.[21]); the representation of social status[26]; the allocation of visual attention to social stimuli[27]; social anxiety[28]; the production of facial expressions[24,29]; social memory[30,31]; and the coordination of autonomic responses that are elicited by social stimuli[32].

Is there a social–non-social division of labour among amygdalar nuclei?

Given that the nuclei of the amygdala have different developmental origins[33–35], and connect via multiple processing loops to different cortical and subcortical areas[36], it is conceivable that anatomically distinct areas of the primate amygdala are specialized to process social signals. However, this speculation awaits experimental verification.

There have been too few nucleus-specific lesion studies in primates to reveal a division of labour among the nuclei. In one study, adolescent monkeys with lesions restricted to the CeA reacted with fewer defensive behaviours to human intruders, showed reduced fear of snakes and had lower levels of stress hormones in the brain and in the periphery compared with control animals[37]. This outcome is expected given that direct projections of the CeA to the hypothalamus and brainstem coordinate the endocrine and energetic or homeostatic aspects of affective behaviour[35].

It would be interesting to compare the outcome of CeA lesions with the outcome of lesions that are restricted to the basolateral nuclei of the amygdala. Indeed, the basolateral nuclei, which primarily include the lateral, basal and accessory basal nuclei, are not directly connected with autonomic and endocrine effectors; rather, they receive inputs from, and send projections to, cortical areas of the brain[36]. The primate amygdala, and in particular the lateral nucleus, receives fewer inputs from the thalamus than the rodent amygdala[35,36], likely because of the dramatic expansion of the cortex in primates. The connectivity of the basolateral nuclei suggests that they evaluate the valence or social relevance of cortically processed stimuli and redistribute the outcome of this evaluation to multiple areas of the cortex. They also project to the central nuclei to initiate the appropriate autonomic responses. Selective basolateral lesions in primates have not been carried out; however, one study showed that pharmacological inactivation of the basolateral nuclei (by local infusion of the $GABA^A$ receptor agonist muscimol) led to a seemingly paradoxical increase in social behaviour that could not be explained by a reduction of social fear[38]. Pharmacological blockade of NMDA-type and AMPA-type glutamate receptors in the basolateral nuclei, however, did not increase social behaviours, likely because excitatory–inhibitory interactions in the microcircuitry of the basolateral nuclei are altered differently when GABAergic versus glutaminergic transmission is manipulated[39]. In summary, based on the literature discussing lesions of and inactivation of the amygdala alone, there is no clear evidence for or against the idea that the primate amygdala is compartmentalized for social behaviours.

Neural specializations for social functions.

In primates, the social deficits caused by amygdala lesions are entangled with non-social deficits, such as the absence of snake fear or reward devaluation[40,41]. These deficits can appear to be more robust and reproducible than social deficits, perhaps because they are easier to detect and quantify compared with spontaneous social interactions. It is also possible that social deficits are a domain-specific manifestation of broader cognitive malfunctions. In this scenario, a monkey who fails to discriminate between unconditioned, negative or positive stimuli (for example, between snakes and food) will also fail to attach value or valence to appeasing or aggressive social displays.

One review[42] made a compelling case that domain-specific social functions are independent from domain-general cognitive functions in the anterior cingulate cortex; that is, the authors cited literature that showed that social functions are not merely a special case of more general functions. Their analysis showed that the social and non-social functions in the anterior cingulate are anatomically and functionally separable, and that further local subdivisions process ‘self ‘ versus ‘other’. It is interesting to consider whether the social and non-social functions of the amygdala can also be detangled.

Social-specific regions of the amygdala could possibly be defined by clusters of face-responsive neurons that exchange signals with neurons in the face patches of the temporal cortex[43]. However, unlike the face patches in the temporal cortex, face-responsive neurons in the amygdala do not appear to be clustered in any particular nucleus or subnuclear region[44]. This point is the case for all other classes of neurons with social correlates, such as the neurons that respond to eye contact[45], parts of the face[46] or social status[26]. Although a few

studies have reported that neurons with particular response properties (some of which indicate social function) tend to be more abundant in certain nuclei or nuclear subregions of the amygdala[47–50], overall there is no obvious and reliable clustering of neurons with social functions in the primate amygdala.

If the anatomical differences between amygdalar nuclei are not reflected in the response properties of individual neurons, then specificity may not be present at the level of individual neurons. It is possible that specificity emerges at a higher level of organization, such as the level of dynamic ensembles of neurons[51,52]. Indeed, the local field potentials recorded with geometrically configured electrode arrays confirm that subnetworks that are spatially restricted to nuclear subdivisions are present in the primate amygdala[53].

Of compartments and species.

Many studies report on elegant region-specific and cell type-specific causal manipulations of the rodent amygdala, a subset of which target social behaviour[54,55]. These studies do not have a primate equivalent, partly because the same optogenetic and chemogenetic techniques have only recently been transferred to primates, and partly because social neuroscience studies in these species have focused on different sensory domains. The typical studies in rodents manipulate olfaction, and the outcome of these manipulations suggests that the social hub of the rodent amygdala is the medial nucleus, where inputs from the vomeronasal organ are processed[56]. By contrast, in primates, olfactory inputs are processed throughout the amygdala[57] but olfaction plays only a small role in social recognition. Indeed, primates do not have a vomeronasal organ, and for social recognition they rely primarily on visual signals that are processed throughout the amygdala, including the medial nucleus[44,45].

Even in rodents, the functional compartmentalization of the amygdala is more evident in non-social experimental contexts[58–61], such as the differentiation of appetitive and aversive stimuli. The compartments are defined by the genetic identity of their neurons, their connectivity and the behaviours that are altered by their selective activation or inactivation (recently reviewed in REFS[9,13]). Importantly, the exquisite details gained from cell type-specific circuit dissection of the rodent amygdala, such as differential encoding of valence by the lateral and medial subdivisions of the CeA, do not align with single-unit activity recorded during valence discrimination[9]. Indeed, neither the genetic identity, connectivity nor response preference for appetitive or aversive stimuli alone is sufficient to label a neuron as having positive or negative valence bias. Different combinations of these features — that is, neurons with multidimensional response properties — can generate relatively heterogeneous neuronal ensembles that may transmit valence preferences more reliably than neurons that are defined based on a single dimension[9].

How many jobs can a neuron hold?

The stimuli and task demands processed by the monkey amygdala are so diverse that almost any task can induce stimulus-related or task-related amygdalar responses (FIG. 1). This diversity reflects the intersection of multiple sensory and cognitive loops in the amygdala. In the social domain, neurons in the amygdala respond to bodies, faces, facial expressions, eyes, gaze direction (reviewed in REF.[21]), social status[26] and the observed or expected

behaviours of social partners[50]. The most common non-social neural correlates in the amygdala include responses to unconditioned stimuli of all sensory modalities across a wide spectrum of valence[62,63]; conditioned sensory stimuli that predict appetitive or aversive outcomes[64,65]; economic decisions[66,67]; and abstract information about cognitive context[68,69].

Multidimensionality (or mixed selectivity) is a reliable feature of neural responses in the primate amygdala that was documented even in early recordings[70]; however, the concepts associated with multidimensionality and its computational importance came into focus only in the last decade. These new concepts are reframing our understanding of the amygdala. Indeed, in humans, non-human primates and rodents alike, many neurons in the amygdala respond to more than one stimulus dimension and task parameter. That is, the activity of a single amygdala neuron typically conveys information about several stimulus dimensions or task parameters. For example, in the monkey amygdala, the same neurons that encode reward value predicted by fractal images also encode the dominance status of familiar individuals[26]. In rodents, the same neurons encode valence and active versus passive behaviours when multiple responses can be given to the same conditioned stimulus[16]. When monkeys perform a task with four variables (specifically, attention to alerting cues, learning the value associated with different stimuli, discrimination of social and non-social stimuli and discrimination between individuals), a large proportion of neurons in the amygdala respond to combinations of two, three or all four variables[17]. The proportion of neurons selective for all four task variables exceeded the level that would be expected by chance (that is, the level expected if the probabilities of a neuron coding for variable A were independent of the probabilities of it coding for variable B), suggesting that a non-random combinatorial scheme gives rise to multidimensional selectivity. Multisensory neurons (that represent an elemental level of multidimensionality) in the primate amygdala follow the same rule: the probability of single neurons responding to multiple sensory modalities is higher than expected by chance[62]. Neurons in the human amygdala also show multidimensional properties: a subset of neurons encode the identity of a visual stimulus and also memory for that stimulus[71]. In light of these findings, I proposed that neurons in the amygdala that respond to faces or eyes should qualify as ‘face cells’ or ‘eye cells’ only if their responses remain selective for faces and eyes in multiple behavioural contexts and after testing with a broad array of stimuli (FIG. 1).

Multidimensional processing

Defining multidimensional selectivity.

It is important to consider whether observations accumulated to date are sufficient to define what a ‘dimension’ is. The term dimension emerged from the computational and analytical methods used to document and quantify this phenomenon, not from theoretical and conceptual advances that preceded experiments and analytical approaches. It appears that any cognitive variable that reliably accounts for variations in the firing rate of single neurons can serve as a dimension. For example, a visual stimulus, an operant behaviour, a reward, the predicted outcome associated with a stimulus, the kinematics of a motor act, abstract variables (such as time, context and memory), and even the level of engagement of the

subject in the task can function as a dimension. Nevertheless, to classify neurons as multidimensional, it is not sufficient to document that they respond to more than one stimulus or task parameter. In technical terms, a dimension can be any arbitrary axis in a multidimensional space (analogous to the '*x*', '*y*' and '*z*' axes in three-dimensional space) as long as the axes are orthogonal (uncorrelated). By representing each dimension on a separate axis, one can build a multidimensional space.

An important and yet only partially resolved issue is whether populations of multidimensional neurons encode linear or non-linear combinations of the different inputs. The terms 'multidimensional' and 'mixed' selectivity have been used interchangeably; these terms do not map onto the linear versus non-linear combination of dimensions that characterize the responses of single neurons, although such a distinction would be desirable. I use the term multidimensional to suggest a large number of non-linear combinations given that linear combinations are likely to saturate with the addition of each new dimension. Indeed, in the social domain, linear combinations of selectivity are difficult to capture, but let us consider a hypothetical neuron that responds to the intensity of a threatening facial expression and the age of the threatening individual; the older the threat-emitting individual and the more intense the threat, the higher the firing rate of the neuron. More often, neurons that respond to individual faces and facial expressions suggest non-linear combination stimulus dimensions[44], as exemplified by the response properties of the neuron shown in FIG. 2.

The distinction between linear and non-linear combinations of selectivity (or mixed selectivity) is important because neurons with non-linear combinations of selectivity can generate higher-dimensional representations than neurons with linear combinations of selectivity[19].

The importance of non-linear mixed selectivity emerged from the analysis of neural responses during multi-alternative tasks, such as the analysis of prefrontal neural activity recorded from monkeys that were trained to recognize or recall specific sequences of images as part of a sequence-learning task[72]. These neurons showed both linear and non-linear mixed selectivity for task parameters and also for multiple stimulus features[18]. When the authors removed the non-linear component of mixed selectivity from every neuron, they could decode every stimulus dimension or task parameter from the population separately using binary decoders. When they removed the linear components (that is, the traditional stimulus selectivity or task selectivity of each neuron), there was sufficient residual information in the population to decode stimuli and task variables at a rate above chance. Based on this and other similar studies, populations of neurons with non-linear, mixed selectivity were argued to generate high-dimensional, abstract representations that are optimal to support flexible behaviours[19]. The reasoning behind this argument is that non-linear mixing allows a downstream area (an area that receives the output from the area that contains the high-dimensional representation) to easily read the required information (akin to a linear decoder)[19]. Unlike linear mixing, non-linear mixing allows choices that depend on latent variables and/or on operations such as exclusive–or (that is, stimulus 1 and not stimulus 2 is rewarded in context A, and stimulus 2 and not stimulus 1 is rewarded in context B). An excellent illustration of this principle was experimentally implemented in a multi-

alternative task that distilled the problem to its essence[68]. In this study, amygdalar neurons were recorded as monkeys learned that one set of conditioned stimuli were rewarded and another set predicted an aversive outcome. This rule held only for a block of trials and was reversed in the subsequent block, but nothing explicit signalled to the monkeys which rule applied during each block. Monkeys used each block of trials as a cognitive context to flexibly and efficiently switch between the appetitive and defensive responses that were appropriate for each context. Note that, in this example, neurons in the amygdala and orbitofrontal cortex encoded the cognitive context (akin to an abstract representation) of the task.

Latent and abstract variables may be difficult to track experimentally, but they are often the critical elements that inform social decisions. Social behaviour relies more often than not on decisions that depend on context or the ongoing pattern of events and interactions, as suggested by the neural responses shown in FIG. 2. Given the hierarchical nature of macaque societies, the status of the displaying individuals determines how substantial and actionable an appeasing or threatening facial expression might be. A mild threat, or even a stern stare from a high-ranking individual, is more consequential than a full-blown threat from an individual of low status. It is more likely than not that the social status and facial expressions would show non-linear mixing. The extent to which neurons in the amygdala show non-linear mixed selectivity remains to be quantified and compared across nuclei, tasks and species. Such analyses are possible because there is robust evidence for mixed selectivity in the amygdala in several multi-alternative tasks that combine multiple behaviours, multiple stimulus categories or decision options[16,17,68].

Advantages of multidimensional processing.

Multidimensional processing contributes to and benefits from learning. Mixed selectivity arises not only from random connectivity (see below) but also as a consequence of learning[73]. This fact was demonstrated by adding Hebbian learning to a model of the prefrontal cortex (built with random connectivity), which resulted in a higher level of mixed selectivity and a better match between the model and the neural data recorded from the prefrontal cortex of monkeys[74]. Conversely, mixed selectivity allows learning that would enable rapid switching between behavioural options[18,68].

Multidimensional selectivity enables the same neurons to be deployed for multiple processes, such that a relatively small number of neurons (only 6 million in the monkey amygdala) can contribute to a large number of cognitive and behavioural functions. Indeed, the number of dissociable outputs of the amygdala may be small compared with the extraordinary richness of the inputs. Consider, for example, the large variety of external stimuli (for example, images, sounds and touch), cognitive processes (such as memory and decision-making) and social events (including conflict or deep attachment) that trigger, via the amygdala, the same judgement of valence (that is, positive or negative valence), the same behavioural responses (for example, approach or avoidance) or the same autonomic responses (for example, changes in heart rate, blood pressure or pupil dilatation). In the framework of multilayered artificial neural networks, multidimensional neurons are quintessential examples of what is ‘hiding’ in the hidden layer. Indeed, dimensionality

expansion by adding layers is a critical step performed in deep neural networks to enhance the accuracy of classifications (that is, of decoding)[75].

Multidimensional processing may also be advantageous to link the basic building blocks of complex behaviours. For example, the social importance of facial expressions exchanged between monkeys depends on the identity of individuals engaged in facial signalling. Accordingly, face-responsive neurons in the amygdala respond to various combinations of identity and facial expression[44] (FIG. 2). In hierarchical societies, each individual has a social status (that is, a rank) and the difference in rank between the signal-emitting individuals and the signal-receiving individuals conveys meaning to the social exchange. It is therefore likely that, in addition to identity and facial expressions, multidimensional neurons also respond to the status differential between social partners. Indeed, neurons in the amygdala do encode the status of individuals[26] and the responses of these neurons span the social–non-social divide, as they also respond to rewards. Similarly, social attention[76] and spatial attention[15] are often processed concurrently because individuals of social interest often change location in space. Under these conditions, neurons in the amygdala may be multidimensional and signal, at the same time, particular individuals and their locations.

Another benefit of multidimensional processing is that, during natural social interactions, it may link neural activity related to ‘self ‘ to neural activity related to ‘other’. Most social processes that are subjected to neurophysiological scrutiny are set up as open-loop situations (for example, monkeys or humans passively viewing images of facial expressions). This approach captures only the social perception component of social behaviour. By contrast, in real-life interactions, social signals are exchanged in perpetual receiving–emitting cycles that are more accurately modelled by closed loops. In a closed loop, the outcome of the current action becomes the input for the next cycle. If the same population of neurons detect and evaluate the incoming social signals and also trigger or coordinate reciprocal behavioural responses, then the loops between ‘self ‘ and ‘other’ can be closed. Indeed, neurons in the amygdala and the motor areas of the anterior cingulate cortex show activity related to both the perception and the production of facial expressions[24]. Likewise, the amygdala contains neurons that respond to the facial expression of others and also neurons that respond to the facial expressions of self[77]. It is unknown, but highly likely (given the high probability that multidimensional processing occurs in the amygdala), that the same neurons respond to both.

Finally, one can add to these advantages of multidimensional processing an advantage that has been often neglected: interfacing interoceptive (or viscerosensory) inputs with affective states. Visceral signals arrive at the amygdala via ascending autonomic pathways from the nucleus of the solitary tract, parabrachial nuclei, the hypothalamus and the insula[36], and probably generate the background on which other ongoing neural processes are grafted[78]. For example, the insula and amygdala in hungry animals bias the visual cortex towards processing visual food cues[79]. Viscerosensory inputs may contribute to global, brain-wide patterns of activity that incorporate into a brain state the state of the periphery and generate coactivity patterns among areas that are not directly interconnected.

Multidimensional processing in other brain areas and cognitive domains.

The high-dimensional representation generated by ensembles of neurons with multidimensional selectivity[19] in the amygdala suggests an overlap in the role of these structures in creating mental states that drive complex behaviours, whether social or non-social[68]. The presence of multidimensional processing in the amygdala, which often captures abstract representations, raises the question of whether the role or roles of the amygdala can be described in terms of simple psychological constructs, such as valence, arousal or relevance detection. The answer seems to be ‘probably not’, because these constructs cannot describe the full dimensionality of these mental states and fail to capture latent, non-observable variables. Neuroscientists have not yet invented a lexicon to adequately denote abstract mental states[80] that morph through various shapes in high-dimensional space. One can speculate that high-dimensional, abstract representations not only allow the selection of behaviourally useful combinations of stimuli but may also facilitate the generation of novel combinations of stimuli that could be useful in new, previously unrehearsed situations. If high-dimensional representations hold the potential for novel combinations, useful to solve new problems, then they might be essential for imagination and creativity.

In retrospect, multidimensional selectivity, with or without the explicit use of this term, has been reported in many brain areas and in multiple behavioural contexts. For example, single neurons in the human parietal cortex show mixed encoding of moving body parts, body side and cognitive strategy (that is, imagined versus executed) applied to movement[81]. A thorough review of the neurophysiological literature, from the perspective of multidimensional selectivity, will probably conclude that unidimensional responses, such as receptive fields, are the exception and not the rule in the brain, and that unidimensional neurons are found mainly in primary sensory areas. Even in the mouse primary visual cortex, however, neurons show multidimensional responses, combining visual information with information about the behavioural and motivation state of the animal[82].

A three-dimensional analogy for such a dynamically changing shape of multidimensional representations is the image of a murmuration of starlings: hundreds or thousands of birds flying together in a cloud that perpetually shifts shape and in which the momentary position of each bird depends on the strength and range of interactions with other nearby birds[83]. Each starling can be considered a ‘neuron’, as a point in three-dimensional space where each axis represents the firing rate in response to three different stimuli or task variables. For example, the three axes could represent the increasing proximity of a social partner, the perceived or predicted aggressive intent of this partner and the facial expressions produced by the receiver. As the social interaction unfolds, this cloud of points moves contiguously through a sequence of states instantiated by the same population of neurons.

Although the emerging framework of multidimensional neural responses and high-dimensional, abstract representation is ideally suited to explore the neural basis of social behaviour, these concepts may inform our perspective in other cognitive domains, too. Certain aspects of the sensory transduction of early sensory processes notwithstanding, it is almost impossible to image how more complex functions of the brain can be carried out efficiently without multidimensional processing.

Large- and small-scale circuits

The contribution of brain-wide circuits.

The intersection of multiple brain-wide processing loops in the amygdala (FIG. 3) may provide the anatomical basis for multidimensional processing. Human studies of resting-state connectivity[84], the task-dependent coactivation of the amygdala with other brain areas (reviewed in REF.[20]), and the application of graph theory to anatomical findings[85] have suggested that the amygdala is one of the subcortical hubs of the brain[86], and specifically the quintessential social hub[20]. Indeed, the amygdala is always on the list of structures in definitions of the social brain[87].

The internal structure and connectivity of the amygdala is best understood from a developmental perspective. Unlike other multinucleate structures, the nuclei of the amygdala originate from different compartments of the developing telencephalon[33–35]. Neurons in the basolateral nuclei (that is, the lateral, basal and accessory basal nuclei) and in all cortical areas originate from the pallium; by contrast, the central and medial nuclei, together with the extended amygdala, develop from the subpallium (which also gives rise to the caudate, putamen and globus pallidus). This distinction is important because the basolateral and centromedial nuclei share cell types, circuit motifs and patterns of connectivity with the cortex and the basal ganglia, respectively.

Despite different patterns of cell migration, neurons of the same origin become more extensively and reciprocally interconnected than neurons of different origins. Indeed, the basolateral nuclei receive and send projections from and to the vast majority of cortical areas (reviewed in detail elsewhere[36]) and contribute as much as, if not more than, the central nuclei to amygdalar output[36]. The central and medial nuclei establish bidirectional connections with an equally numerous list of subcortical structures, including the thalamus, the hypothalamus and the autonomic and homeostatic centres in the brainstem[88–90]. Overall, a complex web of intranuclear and internuclear connections (illustrated in FIG. 3) integrates the signals processed by the cortical and subcortical loops that intersect in the amygdala[91]. Multidimensional processing that emerges from the crosstalk between these loops reflects the spectrum of information processed in the amygdala. Accordingly, a neuron that responds to salient, attention-inducing stimuli, as well as to faces and reward magnitude, may process inputs from the network of cortical and subcortical areas implicated in visual attention[92], from the temporal and prefrontal face-processing areas[93,94] and from reward circuits[95].

The contribution of microcircuits.

The internal architecture of the amygdala constrains the response selectivity of its component neurons. Most cells in the central nuclei are GABAergic and establish inhibitory interactions characteristic of basal ganglia circuits, whereas the cell types (defined based on their molecular, morphological, connectional and functional properties) in the basolateral nuclei are highly similar to those in the cortex[33,96]. These neurons in the basolateral amygdala establish excitatory–inhibitory interactions that seem to recapitulate the interaction patterns between cortical neurons. These interactions shape response patterns along three axes: response magnitude, response duration (promoting phasic or tonic

responses) and response polarity (leading to a decrease or increase of the firing rate)[48,62]. For example, a neuron in the monkey amygdala may discriminate between social and non-social stimuli through its response duration (exhibiting phasic responses to faces and tonic responses to objects) and, at the same time, discriminate between individual faces through differences in the amplitude of the phasic response[48]. These three types of spike-train variations have been shown to discriminate between sensory modalities[62]. Although no relationship was found between a particular spike-train metric and a specific sensory modality (for example, it was not the case that all visual responses were phasic and all tactile responses tonic) in this study, multisensory neurons in the amygdala 'voted' for each sensory modality with a different spike-train metric.

Inhibition and disinhibition play crucial roles in tuning the selectivity of amygdalar neurons, by blocking, reducing or enhancing (through disinhibition) the relative contributions of certain inputs[97] and thus dynamically altering the output of small circuits. The duration of responses elicited by each stimulus might also be modified through inhibition (BOX 1).

For example, multidimensional neurons were commonly recorded from the basolateral nuclei of the amygdala while the monkey was presented with eight different visual, tactile and auditory stimuli[62]. A simplified, hypothetical circuit that generally accounts for the observed changes in firing rate of such multidimensional neurons showed how, even without the inevitable complexities added by the effects of acetylcholine and serotonin, the same neuron could be part of different ensembles that signal attention, sensory stimuli and reward (BOX 1). This simple circuit also helped to reveal the importance of considering the temporal dimension in neural activity: specifically, at two different points, the same neuron (or ensemble) can represent markedly different information about stimuli or context.

Conclusions

The goal of this Perspective has been to discuss the role of the primate amygdala in social behaviour in light of growing evidence that its component neurons have multidimensional responses. There is no evidence for social specializations in the primate amygdala at the nuclear or single-neuron level. On the contrary, it seems that the same neurons contribute to multiple neural ensembles that contain different information at different times. These ensembles may contain abstract or high-dimensional representations to enable flexibility and both social and non-social behaviours. Multidimensional selectivity at the level of the individual neuron therefore reflects the sequential activation–inactivation of brain-wide circuits as the behaviour unfolds.

At first sight, this organizational scheme appears at odds with the known neuroanatomy (that is, the localized destination of inputs and origin of outputs) in primates and the highly compartmentalized view of the rodent amygdala that has emerged from recent cell type-specific circuit dissections. The experimental evidence that supports each view depends, to a large extent, on the advantages and limitations of the approach and techniques used to generate the data. For example, single-cell and ensemble recordings in human and non-human primates are agnostic of the genetic and neurochemical identity of the recorded neurons (although some non-genetic tools recently became available[98]), whereas cell type-

specific tasks in rodents rarely test other sensory modalities or use multi-alternative tasks to reveal multidimensional processing.

The road to better understanding of the amygdala goes through improved technologies and, ideally, technologies that can be shared across species. Note, however, that technological complexity without theoretical sophistication will only generate more data instead of a deeper understanding of the amygdala. The difficulty in answering the question ‘what is the role of the amygdala in social behaviour?’ illustrates the need to move away from defining the role of this complex hub in terms of simple psychological constructs. Progress is likely to come from developing theoretical and computational constructs that can account for both the specificity and flexibility of multidimensional representations at the level of neural populations and their dynamics.

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Box 1 |

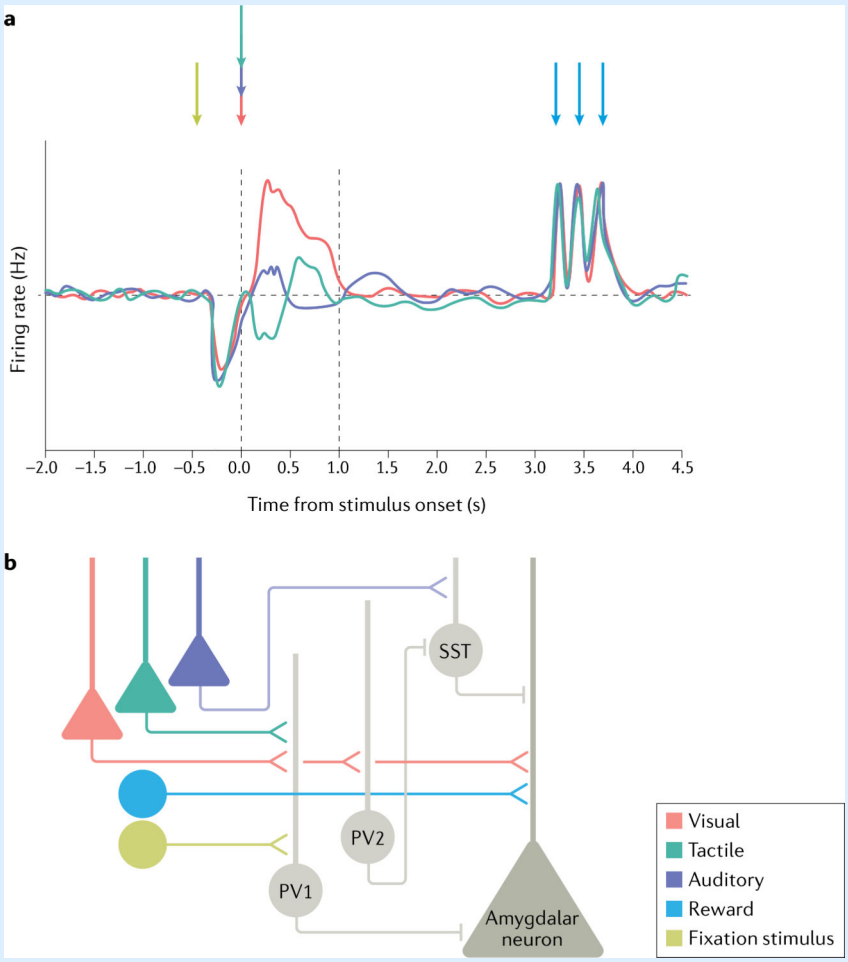
A circuit account for the polarity, size and length of multidimensional responses

Most amygdalar neurons are multimodal Spike density functions of a typical amygdala neuron receiving excitatory inputs for visual, auditory and tactile response, based on data in REF.[62], are shown (see the figure, part a).

In addition to being multisensory, the prototypical amygdalar neuron is also multidimensional as it responds with phasic increases and decreases in activity to alerting stimuli, such as the fixation cue (light-green arrow), sensory stimuli (red, green and purple arrows, representing visual, tactile and auditory stimuli, respectively) and reward (blue arrows) (see the figure, part a).

The patterns of activity seen in this neuron might arise from interactions among different cell types; specifically, the phasic decrease in firing rate at the appearance of the fixation icon (see the figure, part a, light-green arrow) might be explained by activation of GABAergic inhibitory interneurons expressing parvalbumin (PV1 neurons; see the figure, part b) that directly inhibit the soma[129,130].

After successful fixation, one of the sensory stimuli is delivered (see the figure, part a, arrows at time 0). Here, again, inhibition probably helps shape this neuron's distinctive firing responses to different stimuli. For example, the phasic decrease in response to the tactile stimulus (see the figure, part a, green trace) could be explained by the activation of the same PV1 neurons that directly inhibit the soma. visual stimuli might activate the proximal dendrites of the pyramidal cell, causing a phasic elevation of the firing rate (see the figure, part a, red trace), and also activate the PV1 neuron that, through somatic inhibition, shortens the maximal response duration. PV1 neuron-mediated inhibition does not reduce the response to baseline because the visual inputs also activate a second set of GABAergic inhibitory interneurons (PV2 neurons) that inhibit a third type of inhibitory interneuron, somatostatin-positive (SST) neurons (see the figure, part b)[129,130]. the SST neurons tonically inhibit the distal dendrites and the removal of this inhibition, via disinhibition from PV2 neurons, can explain the tonic elevation of firing rate in response to the visual stimulus after the phasic response subsides (around 0.6 s after stimulus delivery; see the figure, part a, red trace). The auditory stimulus causes a small increase in firing rate in the first third of the trial (connection not shown) followed by a decrease in the latter two-thirds of the trial (see the figure, part a, purple trace; each trial lasts 1 s), potentially owing to weak inhibition of the distal dendrite by an SST neuron.



After the sensory stimuli were removed (see the figure, part a, indicated by the second vertical dashed line), the same neuron signalled each juice drop received as a reward, perhaps by activating excitatory neurons (see the figure, part a, blue arrows) that directly contact the pyramidal neuron.

This is only one example of the many interactions that can be set up in simplified circuits. Given that multidimensional neurons can use phasic–tonic distinctions in their responses, the ensemble activity and, implicitly, the specificity of the representation instantiated by that ensemble, can change substantially when the phasic responses decay but the tonic responses are ongoing.

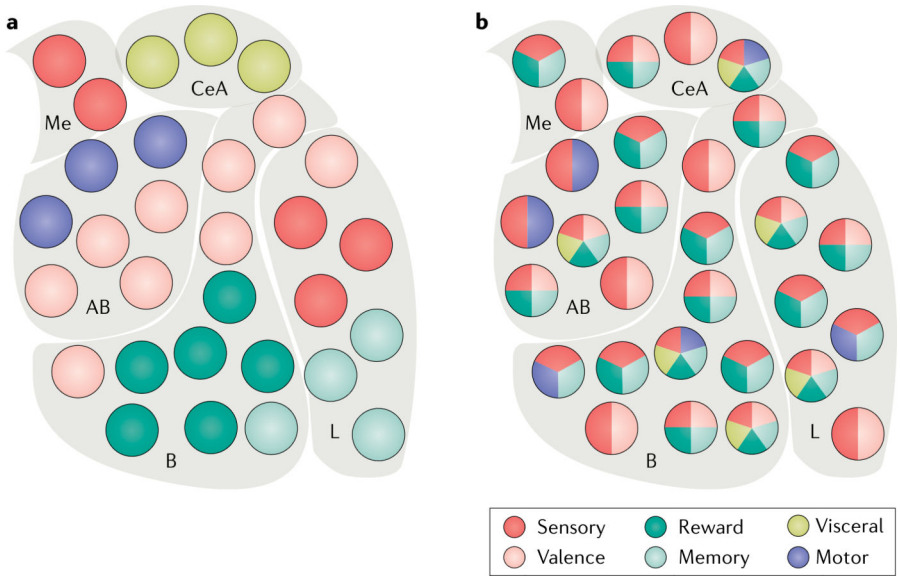


Fig. 1 |. Alternative functional organization schemes of the primate amygdala.
a | One view of primate amygdala organization is that specialized neurons, which are narrowly tuned to a single stimulus or task parameter, form clusters that follow, to some extent, the anatomical target or origin of inputs and outputs, respectively. **b** | An alternative view of primate amygdala organization is that multidimensional neurons are distributed quasi-equally across the nuclei of the amygdala. As indicated in the key, the colours represent a subset of the known stimulus categories that activate the amygdala[16,17,30,64] with the exception of visceral inputs, for which there is limited evidence. The proportion of neurons that respond to each type of input is unknown. AB, accessory basal nucleus; B, basal nucleus; CeA, central nucleus of the amygdala; L, lateral nucleus; Me, medial nucleus.

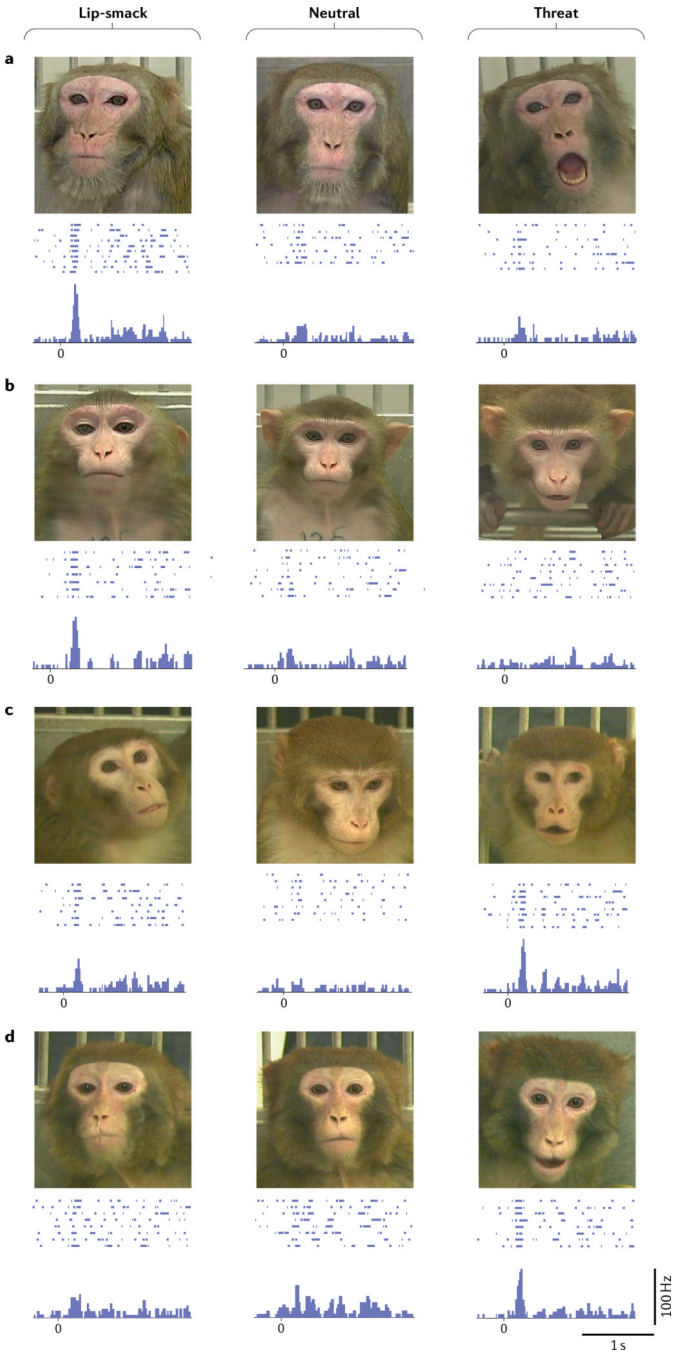


Fig. 2 |. Face-responsive neurons show non-linear combinations of selectivity.

a–**d** | This neuron was recorded from the basal nucleus of the amygdala in response to the passive viewing of face images that represented specific combinations of identity and facial expression. The stimuli in each row of images depict three facial expressions displayed by the same individual. The three columns correspond to appeasing (lip-smack), neutral and aggressive (threat) facial expressions. Rasters (top) and peri-event time histograms (bottom) are shown below each stimulus face and their analysis indicates that this neuron responded to the appeasing facial expression of the monkeys in parts **a** and **b** and to the threatening

expressions of the monkeys in parts **c** and **d**. Analysis of variance showed that there was a significant interaction ($P < 0.001$) between identity and facial expression. Parts **a**–**d** reprinted with permission from REF.[44], American Physiological Society.

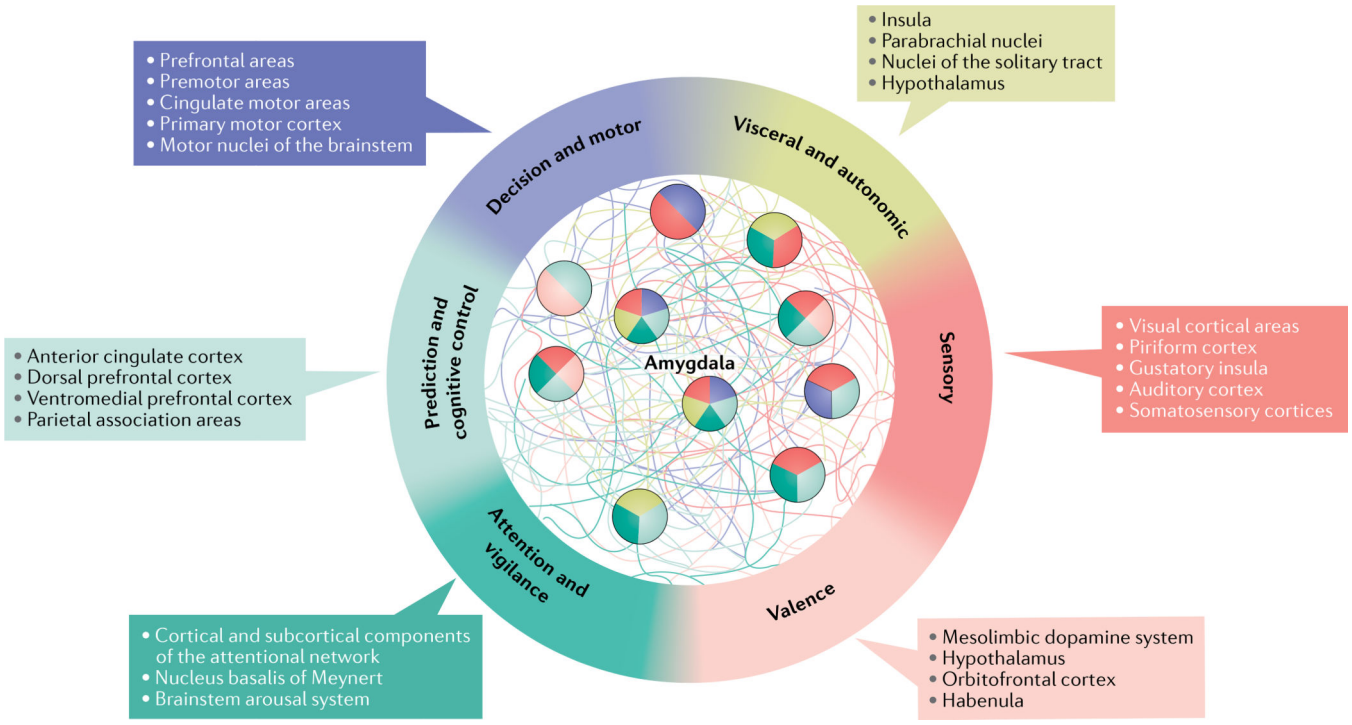


Fig. 3 |. Multidimensional selectivity arises from the intersection of brain-wide circuits.
The amygdala (represented here by the circle in the centre of the image) receives inputs from, and sends outputs to, numerous brain areas, giving rise to a complex web of intranuclear and internuclear connections (as indicated by the coloured lines) and closing circuits that carry out quasi-dissociable functions. The six main functions represented in the ring around the central circle were chosen because they are obligatory components of social behaviours; a truncated list of the brain areas that are connected to the amygdala[36] and involved in the specified function is given in each box. The list of connected areas is by no means complete and does not reflect the level of detail gained from anatomical studies. The multicoloured circles represent multidimensional neurons in the amygdala; each colour represents a stimulus from the brain areas highlighted in the same colour.

Table 1 |

The effects of complete amygdala lesions on social behaviour in monkeys

Deficit	Effect on social behaviour	Species	Age	Sex	Refs
Affective blunting (that is, reduced response to positive or negative social stimuli)	↑	Rhesus	Adult	Mixed	2,99,100
	↑	Rhesus	Infant	Mixed	101
Tameness towards humans	↑	Rhesus	Adult	Mixed	2,22,99,102
Social status	↓	Rhesus	Adult	Males	100
	↓	Vervet	Adult	Males	22
	↓	Stump-tail	Adult	Males	103
	↑	Rhesus	Adult	Males	100
	Ø	Rhesus	Adult	Males	104
Affiliation	↓	Vervet	Adult	Males	22
	↓	Rhesus	Adult	Males	105
Aggression	↓	Rhesus	Adult	Males	4,106
	↓	Rhesus	Infant	Mixed	107
	↑	Rhesus	Adult	Males	100,105
Submissive behaviours	↓	Rhesus	Adult	Mixed	108
	↑	Rhesus	Adult	Mixed	4,109,110
	↓	Rhesus	Infant	Mixed	111
Defensive behaviours	↓	Rhesus	Adult	Mixed	4
	↓	Rhesus	Adolescent	Males	37*a*
	↑	Rhesus	Infant	Mixed	111–115
	↑	Rhesus	Adult	Males	105
	Ø	Rhesus	Adult	Mixed	116–118
Social interest	↓	Rhesus	Adult	Mixed	106,109
	↓	Rhesus	Infant	Mixed	23,110,119
	↑	Rhesus	Adult	Males	9,38*b*,118,120
Attending to social stimuli and responding adequately	↓	Rhesus	Infant	Mixed	108,121,122

Deficit	Effect on social behaviour	Species	Age	Sex	Refs
Spontaneous interactions and reciprocation of social signals	↓	Rhesus	Infant	Mixed	107
	↓	Rhesus	Infant	Mixed	101,123
Sexual and maternal behaviours	↑	Rhesus	Adult	Mixed	2,99,120,124
	↓	Rhesus	Infant	Females	125
Autonomic and endocrine responses	↓	Rhesus	Infant	Mixed	126
	↓	Rhesus	Adult	Males	122,127
Context-inappropriate behaviours	↑	Various	Various	Mixed	22,106,107,128

↑, increase; Ø, no change; ↓, decrease.

[a] The lesion was restricted to the central nucleus of the amygdala.

[b] Pharmacological inactivation only of the basolateral nucleus.