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**Running title: Neural substrates of affect and action in primates**

# Orbitofrontal Cortex and Amygdala Contributions to Affect and Action in Primates

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## I. Abstract

The amygdala and orbital frontal cortex (OFC) work together as part of the neural circuitry guiding goal-directed behavior. This chapter explores the way in which the amygdala and OFC contribute to emotion and reward processing in macaque monkeys, taking into account recent methodological and conceptual advances. Although direct functional interaction of the amygdala and OFC is necessary for some types of stimulus-reward associations, it is not necessary for others. Both regions contribute to the expression of defensive responses to a potential predator. Contrary to the prevailing view, the amygdala and OFC make distinct contributions to emotional responses and reward processing.

## II. Introduction

The ability to learn from experience—that is, to form memories—affords animals an astonishing adaptive advantage. Responding flexibly to the many changes in the environment would not be possible if it all had to be encoded into the genome. Yet memories *per se* provide no benefit; animals benefit from memories only to the extent that they exploit them to make advantageous actions.

So how, in the face of a bewildering array of behavioral options, do animals decide on advantageous actions? Of course, one answer is that they (and we) do not always do so: maladaptive behavior and its causes are major topics in contemporary neuroscience. Yet, often enough, our ancestors succeeded in taking advantageous actions; we would not be here otherwise. This chapter explores the idea that affect mediates the relationship between memory and advantageous action. For the purposes of this chapter, "action" includes responses that are the product of visual choices of objects in addition to actions, *per se*.

In primates, three components of the telencephalon contribute to affect–action relations in a highly direct way: the amygdala, the orbital frontal cortex (OFC), and the medial frontal cortex (MFC). This chapter concentrates on recent research regarding the contributions of OFC and amygdala to affect and action in primates. Monkeys with bilateral ablations of either the amygdala or OFC were assessed for their ability to assign value to stimuli based on reinforcement history, and for their emotional reactions to stimuli. After reviewing the findings, we argue that although the amygdala and OFC functionally interact in mediating some types of adaptive choices, contrary to the prevailing view, the amygdala and OFC make distinct contributions to emotional responses and reward processing. We close with speculation regarding the ways in which OFC and its neighbor MFC might provide complementary contributions to goal-directed behavior.

## III. Neural substrates of affective processing

From the 1960s to the present, neuropsychological studies in nonhuman primates have employed the object reversal learning and win-stay, lose-shift tasks as assays for linking objects with reward. Both tasks require flexible associations of objects with food reward. For example, in the win-stay, lose-shift task, animals must return to an object that had led to food reward in the preceding acquisition phase, and avoid one that did not. The implication was that animals were linking objects with the affective qualities of food reward. Because amygdala lesions produced severe impairment on these tasks, the amygdala emerged as a critical site of stimulus-reward association.[1-6] For decades these findings have been cited as evidence for a general role of the amygdala in stimulus–reward association, which pointed to a key role in affect–action relations. To anticipate the story outlined below, both methodological improvements and conceptual advances have reshaped the landscape in which these and related findings have been interpreted.

Two related developments have altered our view of amygdala contributions to stimulus–reward association as measured by object reversal learning and win-stay, lose-shift. First, we discovered that the effects of axon-sparing excitotoxic lesions of the amygdala in nonhuman primates differed dramatically from the traditional aspirative lesions.[7, 8] The discrepant findings have been attributed to the fact that aspirative removals of the amygdala disrupt both inputs and outputs of inferotemporal visual cortex and perirhinal cortex.[9, 10] Thus, damage to fibers passing near or through the amygdala, rather than loss of neurons in the amygdala, appears to account for many of behavioral deficits observed after the aspirative removals. Improved methods for making selective lesions of deep structures together with the knowledge that the amygdala is not essential for recognition memory functions initially ascribed to it [11, 12] opened the way to a more accurate understanding of amygdala function. Second, there has been a growing awareness that "reward" is not a unitary construct.[13, 14] This has led to the development of new tasks to probe reward processing, including tasks that require the association of objects with either fixed or changing probabilities, magnitudes and values of rewards, as well as the application of traditional learning theory models to begin to discern a more specific role for the amygdala.

Another substrate for affective processing is the OFC. Several neuropsychological studies in nonhuman primates have examined the role of the OFC in tasks such as object reversal learning, tests aimed at assessing behavioral inhibition, and other tasks that relate affect to action. But little of this research took into account the interactions between OFC and the amygdala. Accordingly, this chapter summarizes research comparing the contributions of the amygdala and OFC on a battery of tests of affective processing. All the experiments outlined here examined the effects of bilateral excitotoxic lesions of the amygdala or bilateral aspirative lesions of the OFC

in primates. Where possible, tests of their interaction through crossed disconnections and unilateral lesions are discussed, as well.

### *A. Reinforcer devaluation*

As already indicated, earlier work in nonhuman primates used object reversal learning and win-stay, lose-shift tasks specifically to assess stimulus–reward associations. The underlying assumption was that "reward" in this context reflected the affective qualities of the food. This assumption, however, is without foundation; in these tasks and others, such as discrimination learning set, monkeys can improve their performance in at least two ways: via an object–outcome association (*i.e.*, by choosing the object associated with the food of higher biological value) and via visually-based performance rules (*e.g.*, by choosing the object that is associated in memory with the appearance of a peanut). In the latter case, food provides information independent of its reinforcing value.[15] When monkeys acquire a visually-based performance rule, it allows them to choose efficiently between two objects, only one of which is associated in memory with food. It has been hypothesized that this is instantiated in the form of a prospective memory, laid down at the time of trial x, for the object that should be chosen on the next trial, trial x+1.[16] Although object choices in these circumstances can of course be defined as "stimulus–reward" association, this concept is at odds with what is conventionally meant by reward, namely, information about the biological value of the food.

Given the distinct possibility that previous tests[1-5] relied on visually-based performance rules rather than stimulus–reward value associations, my colleagues and I developed a different assessment of object-outcome associations more specifically: reinforcer devaluation. The task was adapted from work carried out by Hatfield et al.[17] In their experiment, rats learned about sensory cues that reliably predicted the delivery of food reward. Specifically, rats learned to

make conditioned responses, in this case approaches to a food cup, in the presence of a light cue paired with food delivery. After experimental alterations of food value, rats' responses to the food-predicting cue were reassessed in the absence of food delivery. Control rats with central nucleus lesions, but not rats with basolateral amygdala lesions, responded to decreases in food value by reducing the amount of conditioned approaches to the food cup. By applying a similar method in monkeys we hoped to produce a more precise measure of stimulus–reward value association, with the intention of specifically probing the linkage of objects with food value. The test is carried out in two stages. First, monkeys are familiarized with a large number of objects, half of which are associated with one kind of food, designated Food 1, and half associated with a different food, designated Food 2. Second, the value of one food is decreased by feeding it to the monkey, and the effect of this selective satiety on choices between Food-1 and Food-2 associated objects is compared with a baseline condition in which there was no such prefeeding.

In the experiments described here, each experimental group had surgical operations in two stages, with a behavioral test after each stage. In Figure 1, the scores for each group are reflected in a pair of bars: the left bars of each pair show the effects of the first stage surgery (*after first lesion*), and the right bars of each pair show the influence of the complete lesion (*after second lesion*). The control group was also tested twice, but received no surgery. This repeated test design was necessary for assessing the effect of the crossed surgical disconnection of amygdala and OFC (middle pair of bars), and we applied this design to all groups so that their data would be directly comparable.

Intact monkeys avoid choosing objects associated with a devalued food, as indicated by the high devaluation scores obtained by the unoperated control group (Figure 1, left). On average, this group scored slightly better on the second test relative to the first. Scores on the second test

(black bars) reveal that control monkeys shift their choices away from objects associated with the devalued (sated) food by about half, yielding a score of ~17 out of a possible 30. In contrast, monkeys with bilateral lesions of either OFC or the amygdala continue to choose much like they had before the selective satiation procedure. This deficit is reflected in the low devaluation scores obtained after the bilateral removal of either OFC or the amygdala (Figure 1, right), findings recently confirmed by other investigators.[18] Likewise, monkeys with a surgical disconnection that prevents the intrahemispheric interaction of the amygdala and OFC (Figure 1, middle pair of bars) cannot efficiently link objects with the current value of a food reward. Finally, the effects of a unilateral removal of these two structures (Figure 1, second pair of bars) gave an intermediate result. Monkeys with removal of the amygdala and OFC in one hemisphere – either left or right – scored roughly half way between the controls and the other experimental groups. This finding suggests that combined signals from the two hemispheres are summed to influence decisions about object choices.[19]

Control procedures have shown that changes in visual perceptual abilities, food preferences, level of motivation, and satiety mechanisms cannot account for the impairments. For example, monkeys with OFC lesions,[20] amygdala lesions,[21] and crossed disconnection of OFC and amygdala[22] have been found to perform just as much work as intact monkeys to earn food reward, suggesting that the motivation of the monkeys in these operated groups is intact. Nor can nonspecific effects of surgery account for the result; the performance of monkeys with bilateral damage to either the hippocampus or perirhinal cortex is indistinguishable from that of intact controls.[18, 23]

An important feature of the task design was that in the second stage, when monkeys selected between objects after selective satiation, they received only a single trial per pair of objects.

Thus, there was no opportunity to learn the association between the objects and the now devaluated food. The high devaluation scores of intact control monkeys therefore indicates that they were able to automatically integrate the updated food value into existing associations, and this is what the monkeys in operated groups could not achieve. In theory, given enough experience, all the monkeys would have eventually learned to choose objects yielding the food of higher biological value. Consistent with this idea, when monkeys with either OFC or amygdala lesions are given the opportunity to choose between two familiar foods with no objects covering them, like controls, they avoid choosing the sated food.[20, 24, cf. 18] Presumably, during the roughly 30-minute selective satiation procedure, all monkeys, controls and operated alike, are able to acquire the association between the visual properties of the food and the updated value of the food, allowing them to make adaptive visual choices of the food items. That monkeys in the experimental groups are able to avoid choosing sated foods shows that their satiety mechanisms are intact, a finding that serves to further specify the nature of the impairment.

Still, the reinforcer devaluation test outlined above comprises several components: forming object representations, linking those representations with the incentive value of the associated food, registering and encoding a change in the reward value due to selective satiation, linking object representations with those updated values, and using these changed representations to choose between objects. Although, as mentioned earlier, we can rule out effects of the lesions on visual discrimination abilities, several possibilities remain.

Transient inactivation of the amygdala by focal infusion of the GABA agonist muscimol has clarified the mechanisms of stimulus valuation in primates. In these experiments, monkeys received infusions of either saline or muscimol, bilaterally, via cannulae lowered to the basolateral amygdala. The infusions were given either before or after selective satiation. As

expected, when monkeys received saline infusions (either before or after selective satiation) they obtained robust devaluation scores. Similar scores were obtained when the basolateral amygdala was inactivated *after* the selective satiation procedure. By contrast, inactivation of the basolateral amygdala immediately *before and during* the satiation procedure prevented the shift in object choices that normally occurs with selective satiation.[25] Thus, the basolateral amygdala needs to be functionally intact for registration of a change in the incentive value of a food reward and the corresponding shift in the monkey's choices of objects based on food value. Apparently, once the value of the food reward has been updated, no further contribution of the basolateral amygdala is required. [We note this latter finding appears at odds with recent work in rats. Pickens et al.[26] found that after rats had learned stimulus-food associations, the amygdala was not necessary to register changes in the value of the food. Because there are several methodological differences in the test procedures used with rats and monkeys, additional studies will be required to determine the factors responsible for the apparent discrepancy.]

A possible mechanism for this updating function is suggested by neurophysiological studies of awake, behaving monkeys performing a task in which choices of visual stimuli lead to reward delivery. Typically, different visual stimuli are assigned to different types or quantities of juice rewards. Such studies have shown that the activity of OFC neurons discriminates between different rewards: the firing rates of OFC neurons reflect the value of expected rewards largely independently of the spatial and visual properties of the predicting stimuli, and independently of motor-command signals that control the response.[27-29] Taste of the expected reward is also represented, though to a lesser degree. Importantly, OFC neurons appear to code the values of rewards independent of their type and amount, suggesting that the neurons represent value in a common mode.[29] On this basis, it has been suggested that OFC guides choice between "goods".

Another important finding from physiological studies is that the activity of OFC neurons reflects the value of expected outcomes while monkeys are viewing objects (or images), before reward is made available.[28] This type of object-elicited representation of expected outcomes is just what would be needed to guide monkeys' visual choices in the reinforcer devaluation task. Many neurons in the basolateral amygdala of monkeys likewise represent expected outcomes.[30] Interestingly, studies in rats have shown that this type of cue-elicited activity normally observed in OFC neurons is greatly reduced in rats with lesions of the basolateral amygdala. Thus, interaction of the amygdala and OFC underlies at least some aspects of the associative encoding normally observed in OFC neurons.[31]

### *B. Object reversal learning*

Whereas reinforcer devaluation assesses monkeys' abilities to choose between positive objects ("goods") after changes in the value of the food associated with that object, object reversal learning assesses monkeys' abilities to choose between two objects when the reinforcement contingencies are reversed but food values remained unchanged. In this task there are two different objects, one arbitrarily designated the S+ (covering a baited food well) and the other the S- (covering an empty food well). On each trial, a monkey was allowed to choose one of the two objects and, if correct, to retrieve the food reward underneath it. After monkeys learned the original problem, as judged by their ability to consistently approach and displace the rewarded object, the reward contingencies were reversed (starting the next day), and each monkey was trained to the same criterion as before. This procedure was repeated until several serial reversals had been completed. During and after the first reversal, each of the objects available for choice had been associated with reward; hence, reinforcer devaluation and object

reversal learning have in common the requirement to choose between two objects with a history of reward, at least as viewed over the long term.

Figure 2 illustrates the number of errors scored in acquisition of the initial discrimination and during the subsequent seven reversals. Although the groups did not differ in initial learning, some groups were impaired in acquiring the reversals. Specifically, monkeys with bilateral OFC lesions and those with unilateral OFC and amygdala lesions were significantly slower to learn the reversals than intact controls. By contrast, monkeys with bilateral amygdala lesions learned reversals as efficiently as the controls.

Reversals were also analyzed according to a stage of reversal learning (see ref 4). For each session, errors were assigned as follows: stage 1, 21 or more errors; stage 2, 10 to 20 errors; stage 3, 3 to 9 errors. Thus, stage 1 errors occur when the monkey is responding predominantly to the originally reinforced object, stage 2 errors occur when the monkey is near chance performance, and stage 3 errors happen as the monkey progresses from chance to criterion performance. Relative to controls, monkeys with bilateral OFC lesions made significantly more errors only in stage 2. This result contrasts with the earlier report of Jones and Mishkin. They found that monkeys with OFC lesions made an inordinately large number of errors in stage 1, which they interpreted as response perseveration. Because the OFC lesion performed by Jones and Mishkin included the ventral convexity below the principal sulcus (area 12), in addition to the parts of orbital cortex traditionally identified as OFC, the greater deficit after OFC lesions in their report relative to ours probably reflects the larger lesion. When lesions are restricted to the orbital surface of the prefrontal cortex, and limited to the dysgranular and homotypical portions of areas 11, 13 and 14, the deficit is not perseverative, or at least not markedly so.[3,20,32] In future studies it may be profitable to use tasks with three or more choices, which are better able to

identify perseverative errors,[33] or to employ other types of error analyses, ones that can tease apart the way in which monkeys benefit from incorrectly-performed trials (*i.e.*, errors) and correctly-performed trials.[34]

There are at least two possible interpretations of the deficit that follows OFC lesions. First, the most parsimonious account is that a single mechanism underlies performance on both of the OFC-dependent tasks just reviewed: reinforcer devaluation and object reversal learning. On this view, OFC houses representations of expected outcomes, and visual cortical inputs to OFC (from inferotemporal and perirhinal cortex) are the route through which values of expected outcomes are accessed. After OFC lesions, in the absence of representations of expected outcomes, performance on both tasks is impaired. (Although amygdala-OFC interaction is essential for the reinforcer devaluation task, it is important only for updating the values of expected outcomes stored in OFC. Once that process has occurred, the amygdala is no longer necessary for guiding choices of objects based on the updated value.)

An alternative account posits that different mechanisms underlie performance on reinforcer devaluation and object reversal learning, with object reversal learning reflecting application of a visually-guided rule. On this view, the role of food reward is informational rather than hedonic: to signal the current behavior-guiding rule. In our study, OFC lesions did not cause a significant deficit in the early reversals, only in later ones (Figure 2). Indeed, our analysis revealed a significant group x reversal interaction; control monkeys, but not monkeys with OFC lesions, became more efficient at acquiring the reversals with increased experience. Thus, the deficit in the OFC group may be in acquiring a reversal learning set. As discussed earlier, learning set may depend on the ability to lay down a prospective memory about what stimulus should be selected next, when a similar choice arises in the future.[16] If so, then one effect of the OFC lesion – one

underlying the deficit on object reversal learning – may be to disrupt either the acquisition or implementation of a prospective memory mechanism. This second interpretation is in line with the finding that activity of OFC neurons (as well as that of neurons in other frontal cortical regions) reflects behavior-guiding rules[35] and with preliminary data hinting that different subregions within OFC may be responsible for mediating reinforcer devaluation and object reversal learning.[36] This more cognitive interpretation of the results points away from accounts of OFC lesion effects invoking concepts such as perseveration, reward contingencies, and response inhibition, in the sense usually used in animal learning theory and in clinical practice.

Because few visual learning tasks are affected by unilateral lesions in nonhuman primates, it is of particular interest that combined lesions of the amygdala and OFC in one hemisphere were found to yield significant deficits on object reversal learning. To the extent that this signature can be linked to a particular neurotransmitter system or type of learning,[37,38] it may help elucidate the nature of the OFC contribution to object reversal learning.

### *C. Instrumental Extinction*

We employed one additional test of reward processing: instrumental extinction. This task, like object reversal learning, measures monkeys' responses to changing reward contingencies. Unlike object reversal learning, however, there is no alternative response. There are two phases of the test: acquisition and extinction. During acquisition, monkeys were allowed to approach and to displace a single object to obtain the food reward hidden underneath. This behavior was allowed to become well established. During extinction, everything remained the same except food reward was no longer provided. The measure of interest was the number of unrewarded object displacements performed after the reward contingency changed from rewarded to nonrewarded (*i.e.*, the number of responses made in extinction).

To our surprise, we found opposing effects of OFC and amygdala lesions on this task. Whereas monkeys with OFC lesions showed impaired instrumental extinction, monkeys with amygdala lesions displayed expedited extinction (data not shown).[39] The effect of OFC lesions can be considered an increase in impulsivity, although other, more cognitive interpretations remain possible. One interpretation of the deficit after OFC lesions is the same as that offered for object reversal learning: an inability to acquire or apply visually-guided rules in which the appearance of food reward (or not) guides object choices. In addition, the opposing effects of OFC and amygdala lesions suggest that the two structures, under certain circumstances, work via a competitive interaction[40]. Although the nature of the interaction and the degree to which other regions are involved remain to be determined, one attractive possibility is that in the absence of the amygdala, OFC processing of (nonaffective) visual information is more efficient.

### *D. Reactions to an artificial snake*

To examine the contributions of OFC and amygdala to emotion, we used a method adapted from Mineka and her colleagues to assess behavioral reactions to emotionally-provocative stimuli, namely, an artificial snake.[41, 42] In this task monkeys are presented with objects located inside a clear Plexiglas box. We used three classes of objects: rubber snake, rubber spider, and neutral objects. In addition, a food reward is placed on top of the far edge of the box. On each trial, the monkeys were allowed to reach for and to procure the food, which was always located at the edge of the top farthest from the monkey. Thus, this method pits approach responses elicited by food against defensive responses engendered by the snake.

As expected, intact monkeys showed robust emotional reactions to the rubber snake. Whereas intact monkeys quickly reached over neutral objects to obtain the food reward, they hesitated or failed to reach altogether when given the opportunity to reach over the rubber snake

(Figure 3). The facial expressions and movements made in the presence of the snake were mainly defensive, including moving to the back of the cage, eye and head aversion, freezing, and piloerection (Figure 4). The intensity of the defensive behaviors matched closely the description of the snake-naïve monkeys studied by Nelson et al.,[43] in that the monkeys displayed a wide range of behaviors interpreted by human observers as orienting responses, wariness, and fear. These defensive behaviors are the same type of "disturbance behaviors" reported by Mineka and colleagues[41] in snake-naïve monkeys, fully consistent with the idea that snakes induce an innate fear response.

In contrast to the controls, the monkeys with either bilateral OFC or bilateral amygdala lesions displayed relatively shorter food-retrieval latencies on snake and spider trials (Figure 3). In addition, when confronted with the snake, both operated groups displayed fewer defensive behaviors than did the controls (Figure 4). Monkeys with unilateral OFC and amygdala lesions likewise exhibited reduced emotional responses to the rubber snake, and there was no difference in the effects of lesions in the left versus right hemisphere. These data are of interest because they are among the first to show that unilateral brain damage in monkeys is sufficient to disrupt emotional responses. Taken together, our data show that the monkeys with OFC and amygdala damage, unlike controls, had little or no fear of the snake. These data are consistent with the findings of Meunier et al.[44] and Kalin et al.,[45] who reported blunted emotional reactions to fake and real snakes in young adult macaque monkeys following selective bilateral amygdala lesions.

### *E. Reactions to human intruder*

In response to the presence of an unfamiliar human – a "human intruder" – intact monkeys exhibit emotional behavior characterized by defensive, submissive, and aggressive behaviors,[46] many of them different from those elicited by a snake. We included this task to

measure emotional responses to a social stimulus, which would complement our evaluation in the snake test of reactions to a potential predator. The behaviors elicited in response to an unfamiliar human, like those elicited by the snake, are held to be unconditioned responses; they are present early in life and reflect long-term emotional disposition or temperament.[47]

Monkeys were placed in a test cage, taken to a room they had never been in, and left alone for five minutes: the *alone* condition. A human male unfamiliar to the monkey then entered the room, sat approximately 2.5 m away from the cage, and presented his profile to the monkey for five minutes. The human never made eye contact with the monkey during this time: the *no eye contact* condition. After leaving the room for three minutes, the same human intruder returned to the room, sat 2.5 m away from the monkey, and proceeded to fixate the monkeys eyes for 5 min. The human remained motionless and projected a neutral face toward the monkey: the *stare* condition.

The hallmark responses include defensive freezing (especially in the no eye contact condition) and both submission and aggression (especially in the stare condition). Consistent with other published reports,[45] intact control monkeys showed more defensive behavior, especially freezing, in the no eye contact condition relative to the alone condition. In addition, they showed more defensive behavior in the stare condition relative to the alone condition, with a slight increase in aggressive behavior, as well. Relative to controls, the OFC group exhibited more mild aggression during the stare condition (Figure 5). Consistent with the findings of Kalin et al.,[45] monkeys with amygdala lesions did not differ from controls.[cf. 48]

### *F. Conclusions concerning neural substrates of affective processing*

In summary, both the OFC and amygdala are essential for linking objects with the current value of an outcome and for expression of snake fear. Presumably, the valuation process itself

reflects an emotional bias gained through incentive learning.[49] Taken together, these data suggest that these structures necessarily interact in guiding choices of objects and foods based on value signals and danger (*i.e.*, affective) signals. Indeed, in the case of linking objects with current food value, the crossed disconnection experiment indicates the amygdala and OFC directly interact to mediate the reinforcer devaluation effects. By contrast, OFC but not the amygdala is essential for object reversal learning, which, as we have argued elsewhere, [24] does not require processing changes in reward value, but, rather, requires the monkey to apply a visually-guided rule based on the association between the same objects and the presentation of food (*i.e.*, to learn a new reward contingency). Indeed, these data indicate a neurobiological distinction between stimulus–reward associations based on current reward value, as assessed by reinforcer devaluation, and stimulus–reward associations based on reward contingency, as assessed by object reversal learning.

Because we have studied the effects of aspirative lesions of OFC, the work is subject to the criticism that the lesions involve fibers of passage, and behavioral effects of the lesions might therefore be due to damage outside OFC, or in addition to OFC. For example, noradrenergic fibers course long distances within the cortical grey matter;[50] these and other projection fibers traveling in the grey matter would be disrupted by an aspirative lesion. We think it unlikely that damage to fibers of passage caused the behavioral effects in our monkeys with aspirative OFC lesions because selective lesions yield similar behavioral effects. For example, serotonergic depletions within OFC of marmoset monkeys, like aspirative lesions in macaque monkeys, produce a deficit in object reversal learning.[37] Nevertheless, future studies should make use of selective, excitotoxic lesions. In addition, the anatomical connections of different cytoarchitectonic fields within OFC differ, with areas 11 and 13 being preferentially connected

with the amygdala and area 14 being preferentially connected with hippocampus.[51, 52] Consequently, future studies should investigate the functions of subdivisions of primate OFC.

## IV. Models of OFC–amygdala interaction

### *A. OFC vs. amygdala function*

The prevailing, textbook view holds that OFC and the amygdala have the same functions in reward processing and emotion. The idea that OFC and amygdala work together in affective processing, including both emotion and reward, arose from observations that the effects of bilateral amygdala lesions closely resembled those of bilateral OFC lesions. For example, damage to either structure disrupts emotional responses[6, 44, 45, 53-56] and, until our results became available, damage to either structure was also thought to disrupt object reversal learning.[1, 4, 6, 57] Consequently, several investigators have suggested a common circuitry for both emotional responses and reward processing, without distinguishing between the concepts of emotion and reward.[3, 4, 6, 58] Indeed, it has been proposed that emotion is a by-product of received, omitted and expected positive and negative reinforcements.[58] The present findings argue against the textbook view by showing that selective amygdala lesions have no effect on the kind of reward processing required by object reversal learning (Figure 2), although the same lesions in the same monkeys have a clear effect on emotional responses.[56] Thus, OFC and the amygdala make distinct contributions to emotional responses and reward processing, which are distinctly different neuronal processes.

Our results may also inform models of the role of OFC in decision making. OFC is held to represent the value of expected outcomes of goal-directed behavior, and to provide a common currency for the value of a goal, taking into account benefits (*e.g.,* the biological value of food)

and costs (*e.g.,* the time required to obtain the food) thereby enabling organisms to make "good" selections among several possible choices.[29, 59] On this view, the OFC is necessary only for representing the results of a cost–benefit analysis. The basic idea behind this model is that OFC operates downstream from the amygdala for the purpose of decisions and choices, based on predicted rewards. Put somewhat differently, this model holds that the amygdala provides the information needed for OFC to make value comparisons.

Although this idea is consistent with findings from the reinforcer devaluation task (Figure 1), it does not accord with the results from the snake test, in which monkeys must reach over an artificial snake in order to obtain a food reward. If OFC neurons only compute and compare valuation signals, taking into account the positive biological value of the food (a benefit) with the negative biological value of the snake (a cost), we would have predicted that the emotional reactions to the snake, such as freezing or gaze aversion, would be intact after OFC lesions. After all, the amygdala was undamaged and could interact with the remainder of the brain, and the emotional reactions we measured do not depend on cost–benefit computations. This idea did not hold up, however. Instead, OFC lesions severely disrupted emotional responses such as freezing and gaze aversion (Figure 4), as well as producing dramatic reductions in the latency to reach over the snake to obtain food (Figure 3). Importantly, the disruption of emotional responses to snakes cannot be ascribed to an inability to produce these responses. Monkeys with damage to OFC expressed many of the same behaviors in response to the human intruder (Figure 5) that they failed to show in response to the snake (Figures 3 and 4), in amounts equivalent to the controls. Because the amygdala is also essential for marshalling defensive responses to the fake snake, and because amygdala removal, unlike OFC damage, almost completely eliminates the emotional reactions to the snake, the effects of OFC lesions on emotional responses may well

reflect an influence of OFC on the amygdala, although influences in the opposite direction cannot be ruled out. In fact, physiological studies in rodents suggest that OFC makes an essential contribution to the coding of expected outcomes in the amygdala.[31] This issue notwithstanding, the pattern of results argues against a simple model in which the OFC functions solely in cost–benefit analysis and operates downstream from the amygdala (Figure 6A). So in order to understand the neural substrates of affective processing, we must look to a more realistic model of OFC–amygdala interactions.

### *B. A new view*

The old model, illustrated in Figure 6A, implies that reward processing and emotion are more or less the same thing[58] and that the amygdala should therefore be necessary for both reward processing, as assessed by object reversal performance, and emotion, as assessed by emotional reactions such as freezing or gaze aversion. The data discussed above show that view to be untenable. In addition, the old model encompasses the view that OFC, in representing values of expected outcomes, computes only a cost-benefit analysis. Our data indicate that this idea, too, is untenable. To accommodate the findings reviewed here, we propose a new model in which two routes to the OFC, one for visual information and the other for affective information, subserve both emotional responses and reward-driven response choices. On this view, interactions between OFC and both inferotemporal and perirhinal cortex (rather than interactions between OFC and amygdala) allow visual cues to elicit the predicted (long-term) values of food. Based on these and related findings,[60, 61] we think that this network plays an analogous role in tasks in which high-order visual inputs determine the rules for future actions (Figure 6B). By contrast, interactions between the OFC and amygdala would be important for updating the value of expected outcomes and generating appropriate emotional reactions to objects. If true, crossed

surgical disconnections of OFC and the amygdala, on the one hand, and of OFC and inferotemporal cortex plus perirhinal cortex, on the other hand, would be expected to reveal a double dissociation. Crossed disconnection of OFC with inferotemporal cortex plus perirhinal cortex would be predicted to disrupt object reversal learning but not reinforcer devaluation, whereas crossed disconnection of OFC and amygdala would be predicted to disrupt reinforcer devaluation and emotional responses, but not object reversal learning.

The new view allows us to propose an answer to the question posed at the outset: "So how, in the face of a bewildering array of behavioral options, do animals decide on advantageous actions?" Put somewhat differently: How do animals employ their memories to make advantageous decisions? We propose that one aspect of affect – specifically, representations of the expected values of outcomes – provides the link between memory and action. Animals are armed with two mechanisms to realize this link: one dependent on the OFC, considered here, and the other on MFC, taken up in the next section. The first mechanism, the one mediated by amygdala–OFC interactions, allows monkeys to choose advantageously in the face of multiple competing cues, such as objects, assessed on the basis of their past experience and other factors, such as current drive states. Importantly, this mechanism allows animals to make good choices without having to experience the consequences of their actions in their current state. It does so through updating the value of expected food outcomes. Although most published work along these lines involves updating the values of positive outcomes such as food, it is likely that these principles apply equally to updating the value of negative outcomes.[62] This amygdala–OFC mechanism would provide an adaptive advantage by allowing organisms to maximize positive outcomes (*e.g.,* food of high biological value, attainment of desirable sexual partners) and to

minimize negative outcomes (*e.g.,* distasteful or disgusting foods, pain-inducing stimuli) including those that might lead to injury.

## V. Affect and action: the big picture

But how do the current, updated values of food outcomes and other affective signals provide a link between memories and advantageous action? To develop a more complete picture of how affect guides action we must consider two other sets of findings. First, accumulating evidence suggests that MFC, like OFC, represents expected outcomes, taking into account factors such as the magnitude and probability of reward, as well as the effort required to obtain it.[63,64] The precise way in which expected outcomes in OFC and MFC are represented, and potential differences between these regions, is currently a subject of intensive investigation. Whereas OFC is thought to be important for guiding choices among objects or other stimuli, recent research suggests that major portions of MFC are important for guiding choices of actions *per se.*[34, 63, 65-68,69] If so, then the OFC and MFC collectively may guide goal-directed behavior, with OFC linking specific *cues* (including objects) with predicted outcomes and MFC linking particular *actions* with predicted outcomes (Figure 7). On this account, OFC and MFC play complementary roles in using affect (especially the predicted value of outcomes) to guide biologically advantageous action. MFC may also play a role in processing feedback signals used to guide choices.[70] The complex web of interconnections between the lateral and medial parts of OFC, as well as between OFC and MFC,[71] likely reflects the interactions of these systems.

A second part of the "big picture" involves amygdala interactions with sensory cortex. As shown in Figure 6B, the amygdala interacts not only with OFC and MFC to promote adaptive responses, as described above, but also interacts with sensory cortical areas to influence perception. Functional imaging studies have shown that amygdala activity correlates with

enhanced responses to emotionally-charged stimuli in visual cortex, and there is greater functional connectivity between the amygdala and parts of visual cortex (*e.g.*, fusiform cortex) when human subjects view fearful versus neutral faces. Because these effects depend on the integrity of the amygdala and nearby structures,[72] it has been suggested that amygdala-cortical pathways provide a route for increased perceptual processing of biologically significant stimuli. On this view, the amygdala is essential for a top-down influence of emotion on perceptual processing, a kind of "emotional attention". Additional support for this idea comes from a recent physiological study in cats, in which neuronal activity in the basolateral amygdala was found to correlate with increased transmission from the perirhinal cortex to entorhinal cortex.[73] As indicated at the outset, memories are only useful to the extent that animals can exploit them to make advantageous actions; as we have seen, the OFC and amygdala, likely together with related cortical and thalamic networks, process affect to mediate the relationship between memory and advantageous actions.



## VI. Acknowledgments

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## VIII. Figure legends

**Figure 1.** (Top) Ventral views of a standard rhesus monkey brain showing the location of the intended lesion for each operated group (shaded regions). Surgery was carried out in two stages. The group with the crossed disconnection lesion (crossed Amygdala x OFC) also received a section of the forebrain commissures (black line), which was carried out in the same stage as the OFC lesion. (Bottom) Group mean devaluation scores obtained on the reinforcer devaluation task. Error bars indicate ± SEM. The left bar of each pair shows scores obtained after the first stage surgery (either a unilateral amygdala lesion or unilateral OFC lesion). The right bar of each pair shows scores obtained after the second stage surgery. The site of the first surgery was counterbalanced for all operated groups. Each of the operated groups is significantly impaired relative to controls. Unoperated controls (N = 10); Unilateral amygdala & OFC lesion (N = 8); Crossed amygdala X OFC lesion (N = 4); Bilateral amygdala lesion (N = 5); Bilateral OFC lesion (N = 4).

**Figure 2.** Group mean errors to criterion for initial learning of a single pair object discrimination problem (Init) and seven serial reversals (R) in the object discrimination reversal learning task. Error bars indicate ± SEM. Unoperated controls (N = 10), diamonds; monkeys with bilateral OFC lesions (N = 3), triangles; monkeys with bilateral amygdala lesions (N = 5), squares; monkeys with unilateral amygdala and OFC lesions (N = 8), circles. A, amygdala.

**Figure 3.** Group mean food-retrieval latency (sec) during exposure to an artificial snake (Snake trials) and neutral objects (Neutral-object trials) across five sessions. Error bars indicate ± SEM. Unoperated controls (N = 10), diamonds; monkeys with bilateral OFC lesions (N = 4), triangles;

monkeys with bilateral amygdala lesions (N = 5), squares; monkeys with unilateral amygdala and OFC lesions (N = 8), circles. A, amygdala.

**Figure 4.** Group mean cumulative duration (sec) for defensive (top) and approach (bottom) behaviors during exposure to an artificial snake. Error bars indicate ± SEM. Unoperated controls (N = 10); monkeys with bilateral OFC lesions (N = 4); monkeys with bilateral amygdala lesions (N = 5); monkeys with unilateral amygdala and OFC lesions (N = 8). A, amygdala.

**Figure 5.** Group mean cumulative duration (sec) of aggressive behaviors in the three conditions of the human intruder task. Aggressive behaviors included both mild and high aggressive behaviors such as mouth threat, ears back, and cage shake. Error bars indicate ± SEM. Unoperated controls (N = 10); monkeys with bilateral OFC lesions (N = 4); monkeys with bilateral amygdala lesions (N = 5); monkeys with unilateral amygdala and OFC lesions (N = 8). A, amygdala.

**Figure 6.** (Top) The old model incorporates ideas derived from both neuropsychological findings from the 1960-1980s as well as from contemporary neuroeconomics. The model indicates a joint role for the OFC and amygdala in stimulus-reward association and emotion, with no distinction between emotion and reward processing. Also according to this model, the sole function of the OFC is computation of a cost-benefit analysis that serves to guide decisions. Neither view can account for the data reviewed here (see text for explanation). (Bottom) The new model suggests that both the amygdala and IT/PRh interact with OFC to guide decisions. In addition, each structure interacts with each of the others. For example, the amygdala can

modulate activity in IT/PRh to enhance sensory processing of biologically significant stimuli and events. IT, inferotemporal cortex; PRh, perirhinal cortex.

**Figure 7.** (Top) Neural circuits involved in goal-directed action based on visual sensory inputs. Neurons in OFC and MFC represent the values of expected outcomes, which can be updated via interaction with the amygdala. The OFC likely plays a major role in guiding choices of objects whereas the MFC likely plays a major role in guiding choices of actions. Both OFC and MFC make an essential contribution to making advantageous decisions. (Bottom) Lateral and medial views of a macaque brain showing the approximate locations of A, OFC, MFC, IT and PRh, as well as their interconnections. A, amygdala; IT, inferotemporal cortex; MFC, medial frontal cortex, PRh, perirhinal cortex.

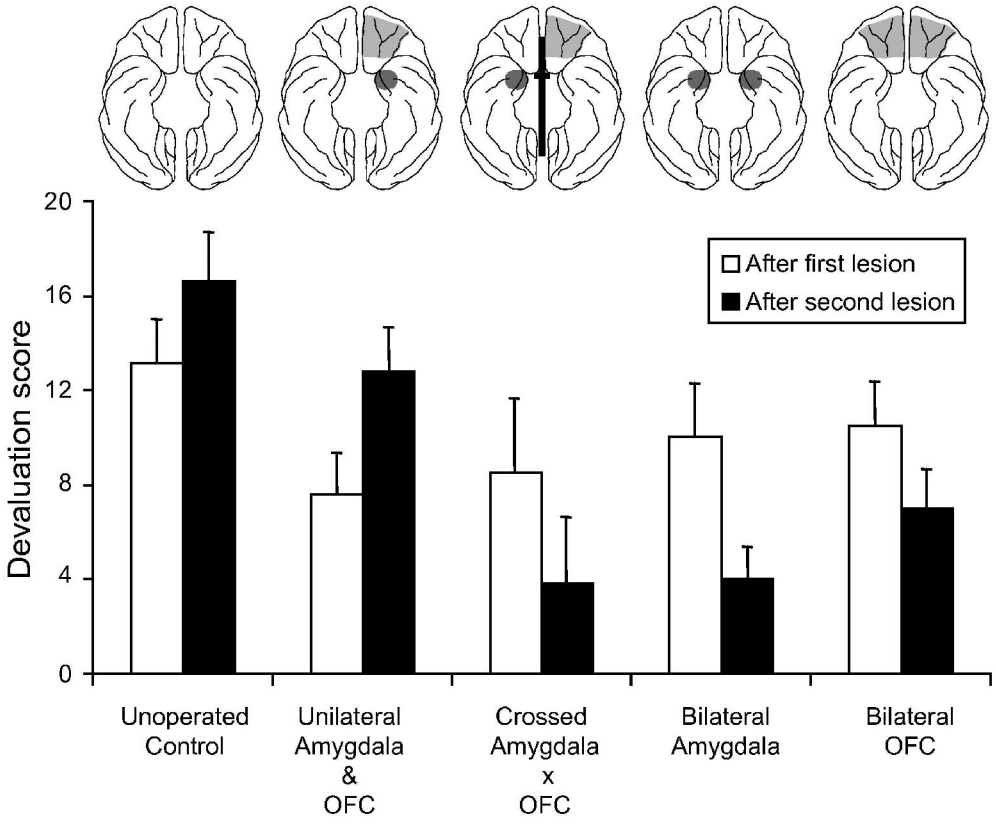


**Figure 1**
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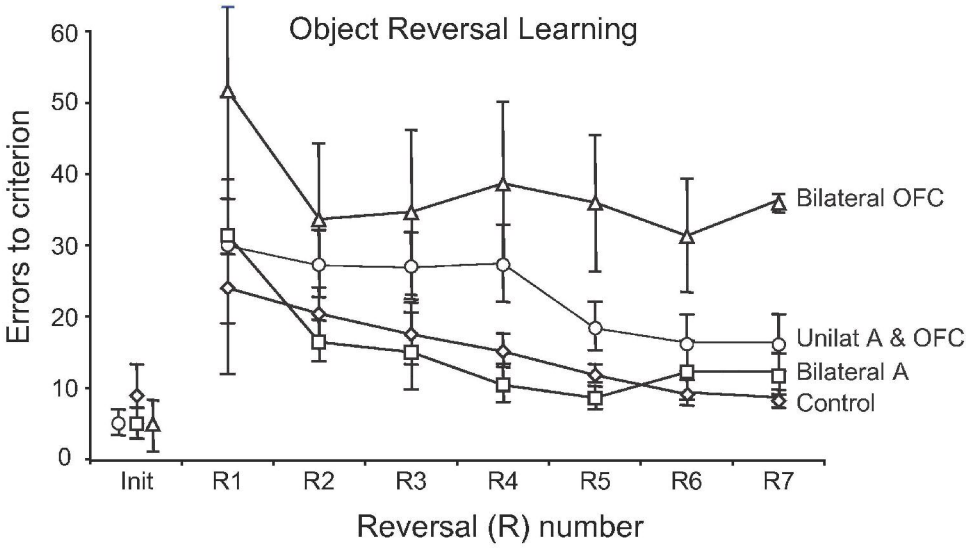


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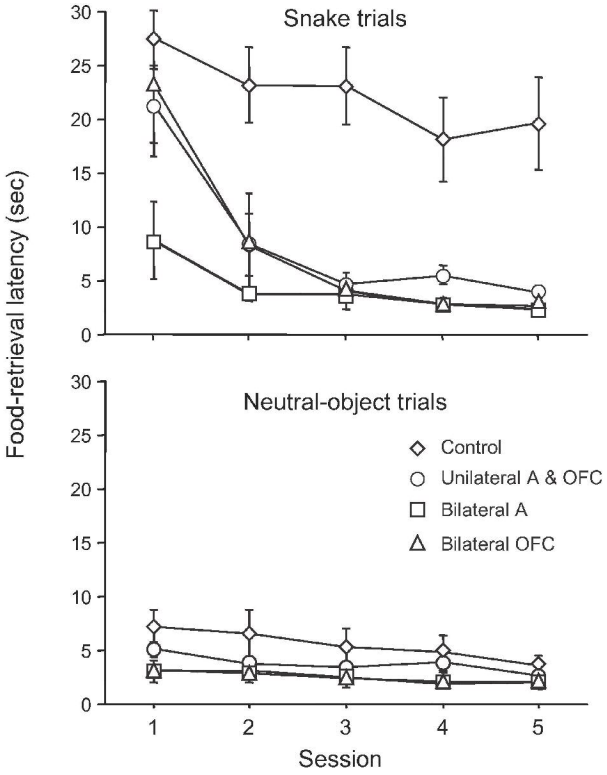


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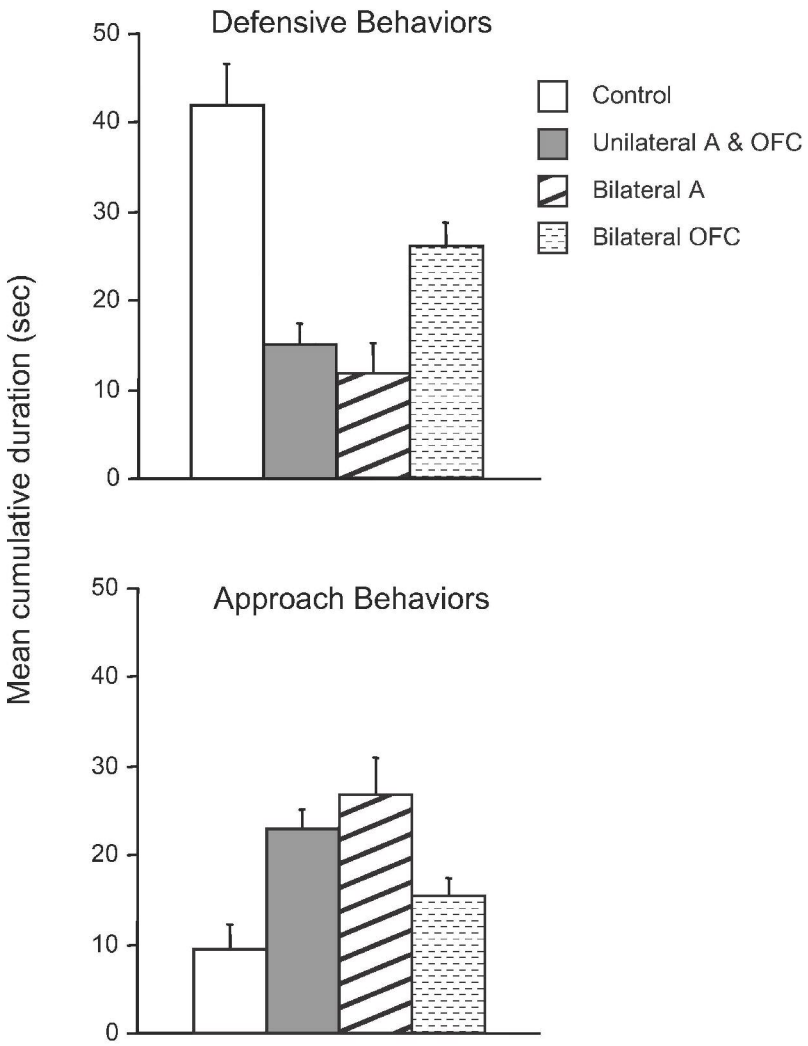


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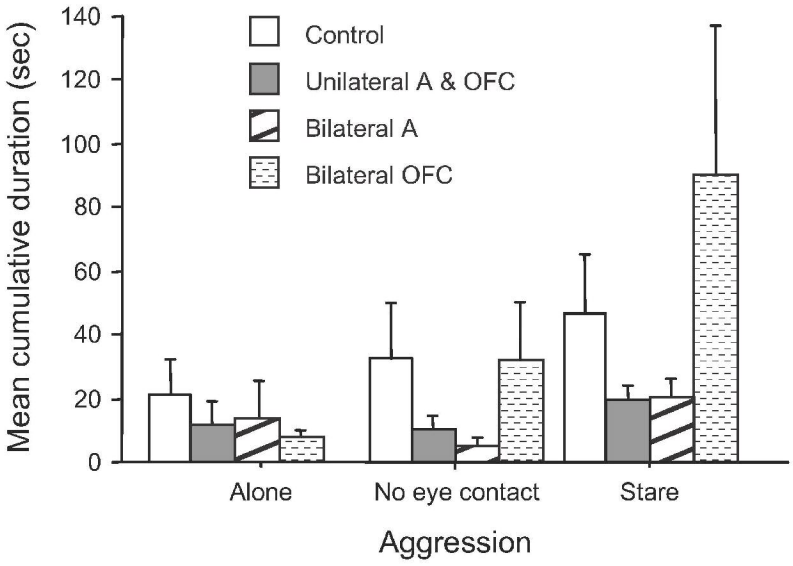


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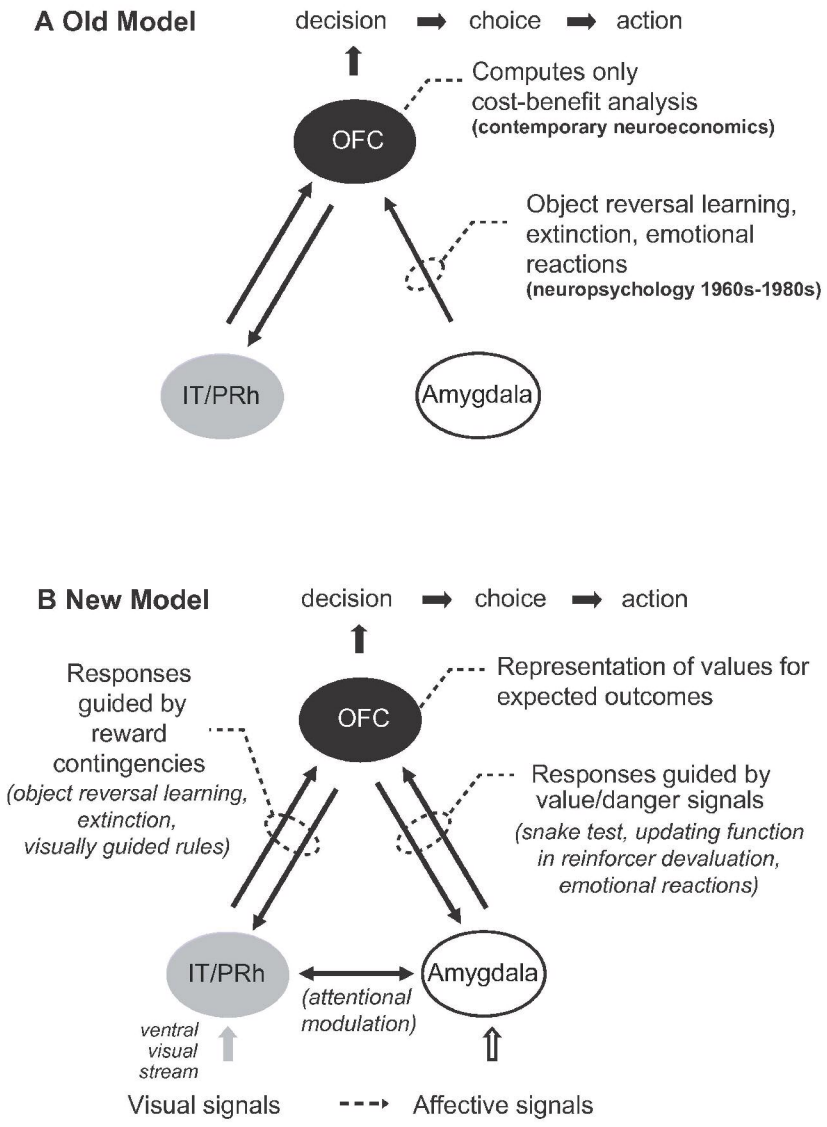


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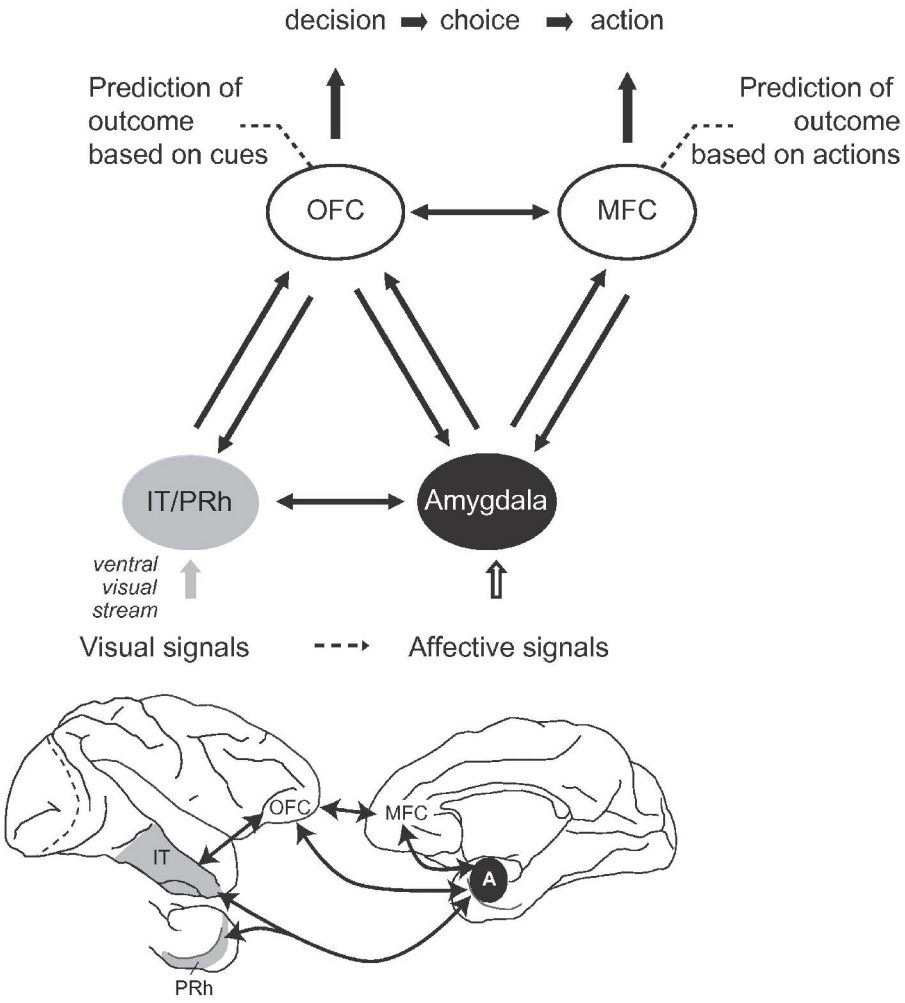


**Figure 7**
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