Interactions between orbital prefrontal cortex and amygdala: Advanced cognition, learned responses and instinctive behaviors

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Abstract

Recent research indicates that the orbital prefrontal cortex (PFo) represents stimulus valuations and that the amygdala updates these valuations. An exploration of how PFo and the amygdala interact could improve the understanding of both. PFo and the amygdala function cooperatively when monkeys choose objects associated with recently revalued foods. In other tasks, they function in opposition. PFo uses positive feedback to promote learning in object-reward reversal tasks, and PFo also promotes extinction learning. Amygdala function interferes with both kinds of learning. The amygdala underlies fearful responses to a rubber snake from the first exposure on, but PFo is necessary only after the initial exposure. The amygdala mediates an arousal response in anticipation of rewards, whereas PFo sometimes suppresses such arousal. A role for PFo in advanced cognition, for the amygdala in instinctive behavior, and for cortex-subcortex interactions in prioritizing behaviors provides one account for these findings.

Introduction

> In no case is an animal activity to be interpreted in terms of higher psychological processes, if it can be fairly interpreted in terms of processes which stand lower in the scale of psychological evolution and development. [1, p. 59]

According to Morgan's canon, quoted above, accounts of behavior lowest on the "scale of … evolution" should always prevail. But contemporary biology has resoundingly discredited the concept of an evolutionary scale, and Morgan's canon too often leads to a psychology that differs little from behaviorism, if it does so at all. Although behaviorism is "all but dead" as a philosophical matter [2], many neuroscientists still become unduly suspicious when accounts of behavior invoke concepts beyond the behaviorist trinity of stimuli, responses and behavioral outcomes. Here we reject such skepticism, along with Morgan's canon, in order to interpret recent findings on the orbital prefrontal cortex (PFo) and the amygdala in terms of advanced cognition and innate behaviors, as well as stimuli, responses and outcomes. By advanced cognition, we mean learned behaviors such as strategies, high-order rules and learning sets that transcend credible accounts in terms of the behaviorist trinity. By innate behaviors, we mean unlearned, inborn behaviors characteristic of a species, including unconditioned autonomic responses and valuations of biological importance.

After summarizing selected findings on the neural substrates of reward processing and affect in primates, we discuss them in three sections: one each on amygdala function, prefrontal

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function and cortex-subcortex interactions. As an example of cortex-subcortex interactions, we begin with a consideration of those between PFo and the amygdala.

Orbital prefrontal-amygdala interactions

Recent findings have revealed both cooperative and contrasting functions of PFo and the amygdala. Results from the *devaluation task* point to a cooperative function. This task assesses an animal's ability to link objects or other biologically neutral stimuli with reward value. Typically, the task begins when animals consume one kind of food to satiety, thus devaluing it. Later, they choose between a stimulus associated with the devalued food and a stimulus associated with a different food. Intact rats and monkeys avoid choosing stimuli associated with the devalued food, a finding called the devaluation effect; animals with amygdala lesions typically fail to show this effect [3,4,5,6]. For example, macaque monkeys with bilateral amygdala lesions (Fig. 1a, red) choose objects associated with the devalued food more often than controls (Fig. 1a, black). Bilateral PFo lesions (Fig. 1a, blue) and surgical disconnections that disrupt PFo-amygdala interactions (Fig. 1a, green) have the same effect, but damage elsewhere in prefrontal cortex does not [7•,8•] (Fig. 1b). Importantly, the monkeys with PFo and amygdala lesions perform poorly only when choosing between objects; when choosing between the two foods they successfully avoid the devalued one. In monkeys, reversible inactivation of the amygdala *during* the selective satiation procedure, not afterward, disrupts the devaluation effect [9]. This finding indicates a role for the amygdala in updating food values as animals approach satiety during feeding.

Other results point to contrasting roles for PFo and the amygdala. In the *serial object-reversal learning task*, macaque monkeys learn to choose a previously unrewarded object and to avoid a previously rewarded one. During this task, PFo and amygdala lesions both influence the use of positive feedback, but in opposite ways [10••]. PFo lesions cause a deficit in using positive feedback (Fig. 2a, blue), whereas amygdala lesions lead to an improvement (Fig. 2a, red). In contrast, monkeys with both kinds of lesions use negative feedback nearly normally [10••, *cf.* 11].

Three additional tests also reveal contrasts in PFo and amygdala function: the extinction task, the snake test, and Pavlovian conditioning. Like serial object-reversal learning, the *extinction task* involves changes in object-reward associations. Initially, displacement of an object produces a reward, but the extinction task rescinds this association. In macaque monkeys, PFo lesions delay the extinction of object displacement (Fig. 2b, blue), whereas amygdala lesions speed extinction (Fig. 2b, red) [12]. These findings show that PFo function promotes this kind of learning and that amygdala function interferes with it.

In the *snake test*, macaque monkeys need to reach over either a neutral object or a rubber snake to retrieve food. Food-retrieval latency quantifies fear in the presence of the snake, which appears once per day in a series of trials administered every other day for five days. On trials with neutral objects, all monkeys retrieve the food quickly (data not shown). On 'snake trials', control monkeys retrieve the food slowly, if at all (Fig. 2c, black). After PFo lesions, monkeys reach for the food quickly (Fig. 2c, blue), as do monkeys with amygdala lesions (Fig. 2c, red) [13,14]. The important finding is this: for PFo lesions—but not for amygdala lesions—this abnormally fast food retrieval occurs only after an initial exposure to the frightening object.

In *Pavlovian conditioning*, a conditioned stimulus (CS) predicts the occurrence of a future unconditioned stimulus (US). For example, the sight of food (CS) can indicate its later availability (US). In this situation, marmosets with amygdala lesions show impaired anticipatory autonomic responses to imminent food availability (Fig. 3a) [15]. In another example, a tone (CS) can indicate the future availability of a food reward (US). Then, on a

probe test in which the CS stops and the predicted reward fails to appear, marmosets with PFo lesions maintain an abnormally high level of arousal (Fig. 3b) [16••].

Amygdala function

The amygdala appears to link stimuli to innate behaviors, including autonomic responses. This idea accounts for the most well known amygdala function, fear conditioning, which involves associating an initially neutral stimulus, a CS, with innate (unconditioned) fear responses [17]. Can the amygdala results presented here be understood in that framework?

Like fear conditioning, the devaluation effect involves linking an initially neutral stimulus with an innate response: an unlearned valuation response. In this case, the valuation response reflects the decreased value of a food as animals consume it to satiety and includes the affective responses generated by that valuation. The valuation response is unlearned in the sense that animals do not have to learn that a food becomes less valuable with satiety or that they should produce a certain autonomic response on that basis. Because amygdala-PFo interactions underlie the choice of objects leading to high-value foods (Fig. 1a), and because the amygdala is only necessary during the devaluation (satiety) process [9], the amygdala appears to update representations of food value stored elsewhere, including PFo. We view such updated representations as memories of the instinctive valuation responses generated by the amygdala.

Indeed, updating valuations could be a general amygdala function. For instance, when response outcomes involve two or more foods, updated valuations depend on the basolateral amygdala [18], with the updating tied to each food's specific sensory qualities. In contrast, the central nucleus of the amygdala conveys updated value in a more general sense, one independent of a food's specific sensory qualities [19]. Updating can also explain the influence of rewarded stimuli on tests of Pavlovian-to-instrumental transfer (PIT). For central-nucleus dependent tasks, lesions of the nucleus accumbens core (but not shell) disrupt PIT [20], whereas for basolateral-dependent tasks, shell (but not core) lesions have that effect [21]. Updated valuations provided by the amygdala to the nucleus accumbens probably mediate these two effects. In another aspect of stimulus valuation, called salience or emotional attention (Fig. 4), the amygdala appears to enhance the processing of emotional facial expressions in visual cortex [22]. In accord with the foregoing discussion about PFo, this phenomenon could reflect another aspect of linking updated valuation responses, generated by the amygdala, to sensory representations elsewhere.

A role for the amygdala in innate valuation responses could also account for results from the reversal, extinction and snake tests. In the first two cases, amygdala function contributes to linking neutral objects with positive affective responses; in the third case it contributes to linking a frightening object to negative affective responses. The reversal [10••,11] and extinction [11,12] tasks invite responses to objects linked to positive affective responses, which reflect experience prior to the change in object-reward contingencies that occurs in both tasks. Removal of the amygdala could enhance task performance (Fig. 2a,b, red) by making it easier for the monkeys to avoid objects that would, were the amygdala intact, produce positive affective responses. This idea also accounts for the finding, in rats, that basolateral amygdala lesions abolish reversal impairments induced by lesions of the agranular orbitofrontal cortex [23]. In the snake test, disrupting the linkage of stimuli with negative affective responses leads to faster, relatively fearless food retrieval (Fig. 2c, red).

Prefrontal function

The granular prefrontal cortex (PFg) stores knowledge about ordered sequences of events and actions played out over various time frames [24]. This knowledge plays a central role in acquiring strategies, learning sets and high-order rules, along with other aspects of advanced

cognition [see ref. 25 for a consideration of high- vs. low-order rules]. Accordingly, PFg lesions cause deficits in behaviors guided by high-order rules and strategies [7•,26,27,28••], as well as learning sets [29•], which involve the use of rules and strategies to speed new learning. PFg functions both in new learning about events and actions distributed over time, as well as the recall of rules and strategies based on these events [29•,30••,31••,32].

PFo is a key part of PFg. It represents valuations of biological importance [33,34,35], which object representations can access via multimodal sensory inputs to PFo. For objects, inputs from inferotemporal and perirhinal cortex play an important role in creating these linkages. PFo also receives direct inputs from the amygdala, as well as relatively direct inputs from olfactory, gustatory and visceral cortex. Thus, inputs to PFo have a unique pattern of convergence that makes PFo ideal for linking stimuli to outcomes. There is, however, no reason to assume that its functions are limited to linking predicted outcomes with simple representations, such as those for sensory stimuli or stimulus sequences. In advanced cognition, an analogous process could create linkages between outcomes and high-order rules [36], strategies or learning sets. Can this idea account for the PFo results presented here?

In the snake test, monkeys with PFo lesions perform fearfully, like intact monkeys, on the first exposure to the rubber 'snake', but later act relatively fearlessly, like monkeys with amygdala lesions (Fig. 2c, blue). We think that this could occur because PFo learns about the outcome of response strategies in the overall testing situation, as opposed to learning about stimulus-outcome associations on a trial-by-trial basis. According to the present account, both PFo-lesioned and intact monkeys avoid the 'snake' on the first exposure because of the risk involved and the associated affective response (as signaled by the intact amygdala). The first 'snake trial' teaches intact monkeys that they can obtain a reward with only a modest cost in terms of delay and still avoid the frightening object. Thus, they forego taking food on subsequent 'snake trials' because they *know* that food can be obtained on a safe, neutral-object trial that will soon follow. Monkeys with PFo lesions never learn this more sophisticated response strategy and so their behavior is dominated by simpler factors, which lead to delay intolerance and rapid food retrieval, 'snake' or no 'snake'.

PFo enhances the use of positive feedback to make correct choices after object-reward reversals (Fig. 2a, blue), and this finding, too, might be explained in terms of rules, strategies and learning set. We think that PFo uses positive feedback to evaluate and implement a form of learning set called a *reversal set*: the ability to shift choices quickly between two objects that depends on experience with previous reversals. Indeed, object valuations based on prior experience interfere with performance immediately after reversals, and a reversal set helps overcome this problem. This idea complements a previous one about the anterior cingulate cortex (AC). In a study of *action*-reward reversals, as opposed to the *object*-reward reversals discussed so far, Kennerley et al. [37] found that AC lesions impair the use of positive feedback to stay with correct actions. It also complements two other findings about PFo: PFo lesions disrupt choices among three objects when reward follows a dynamic, stochastic schedule [38••] and they also cause impairments in switching between well-learned rules [28••]. Taking these results together, we think that reward feedback in PFo (and AC) performs several functions. It guides the evaluation of stimuli (PFo) and actions (AC), but it also guides the evaluation of response rules such as a reversal set. Aversive feedback, also available in PFo [34], could function similarly, but not through response inhibition, as generally assumed. Instead, the greater importance of positive feedback *vs.* negative (nonreward) feedback in the reversal task [10••] argues against response inhibition and perseveration as useful concepts in understanding PFo function. As usually construed, failures of response inhibition result from a deficit in using negative feedback to switch from a given response, thus causing perseveration. Instead, we think that PFo contributes to the assignment of value to the reversal set, along with each of the choice objects.

PFo-mediated cognition could also account for results from the extinction task (Fig. 2b) and Pavlovian conditioning (Fig. 3b). Knowledge about the overall testing situation would speed "extinction" once intact monkeys learn that food availability does not follow object displacement. The distinction here is between *knowing* that reward will not appear and the suppression of a reflex-like stimulus-response association. Monkeys with PFo lesions would, according to this account, persistently displace the object (Fig. 2b) because they lack certain knowledge. In this case, for example, monkeys with PFo lesions would be unable to apply a rule such as "unrewarded objects remain unrewarded." Similarly, for Pavlovian conditioning, we think that PFo stores knowledge about the many circumstances that do not involve rewards. Recall that in the experiment described above, a tone CS predicts reward, which becomes available during tone presentation. In a probe trial, however, the tone turns off and the reward fails to appear. According to this account, PFo suppresses anticipatory autonomic arousal after 10–20 s, once monkeys recognize the low-value context signaled by the absence of both the CS and the predicted reward. PFo lesions cause a more persistent arousal (Fig. 3b) because of the loss of knowledge about this low-value context.

Cortex-subcortex interactions

PFo and amygdala interactions occur in the context of cortex-subcortex interactions, generally (Fig. 4). According to Petrovich and Swanson [39], hippocampus-amygdala interactions prioritize the expression of competing innate behaviors, such as feeding and defensive behaviors. This function could explain the role of hippocampus in enabling snake fear on the second and later exposures [40] and in choice behavior based on an animal's current motivational state (*e.g.*, hungry *vs.* thirsty) [41,42]. Hippocampus-amygdala interactions can be viewed as one aspect of cortical-subcortical interactions.

According to the scheme presented in Figure 4, the agranular frontal cortex interacts with subcortical structures to prioritize behaviors based on learned associations among stimuli, responses and outcomes and overrides innate behaviors that also compete for control of behavior (Fig. 4, green) [43]. As an example of the latter, the matching-to-position task requires rats to surmount an innate tendency to avoid recently exploited foraging sites. Intact, control rats learn to surmount that instinctive tendency, but lesions of the medial agranular frontal cortex disrupt this learning [44].

Medial frontal cortex also prioritizes competing conditioned behaviors (Fig. 4, brown). Rats with AC lesions show deficits when two or more stimuli vie for control of behavior [45,46] and when two or more actions compete based on cost-benefit tradeoffs [47,48,49]. Another medial frontal area, prelimbic cortex (PL), biases behavioral control toward goal-directed (R–O) associations, whereas infralimbic cortex (IL) biases behavior toward outcome-independent, S–R associations (habits) [50]. These lesions limit the ability of rats to switch nimbly between competing behaviors. Inactivation of PL + IL cortex does not, however, affect the ability of rats to switch between two other competing conditioned responses, one based on extrinsic coordinates (*e.g.*, "go North") and the other based on intrinsic coordinates (*e.g.*, "go left"). Such inactivation does, however, disrupt the ability of rats to use the most recently learned response 24 hours later [51•], which reflects a problem in retaining competing behaviors. Other parts of the agranular frontal cortex also bias the selection of competing behaviors [52,53,54, 55]. For example, inactivating the agranular orbitofrontal cortex (OFa) leads to poor retention of reversals within (but not between) coordinate frames [56••].

Figure 4 also depicts PFg, which includes PFo, as prioritizing behaviors that depend on advanced cognition, such as competing high-order rules and strategies, as well as competing internal *vs.* sensory influences over behavior [57,58]. Consistent with a role in advanced cognition, the areas composing PFg are primate innovations, whereas most if not all mammals

share the agranular frontal areas mentioned above [59]. PFo probably mediates its prioritizing function in part via corticostriatal signals that establish task sets [60].

In addition to prioritizing advanced behaviors, PFg also functions to surmount behaviors that depend on conditioned associations among stimuli, responses and outcomes, and also to surmount instinctive behaviors (Fig. 4, blue). For example, to develop a learning set monkeys surmount conditioned associations by using various strategies, including knowing what information to retain in working memory [29•,61].

Conclusion

The findings featured here point to both cooperating and contrasting functions of PFo and the amygdala. Cooperation arises when PFo depends on the value-updating function of the amygdala, whereas contrasting functions reflect, among other things, PFo's role in surmounting behaviors that depend on the amygdala. In rejecting Morgan's canon, we have discussed PFo-amygdala interactions in terms of both advanced cognition and innate behaviors, in addition to conditioned associations. Likewise, future research should embrace accounts of animal behavior that extend beyond the behaviorist trinity of stimuli, responses and outcomes.

Acknowledgments

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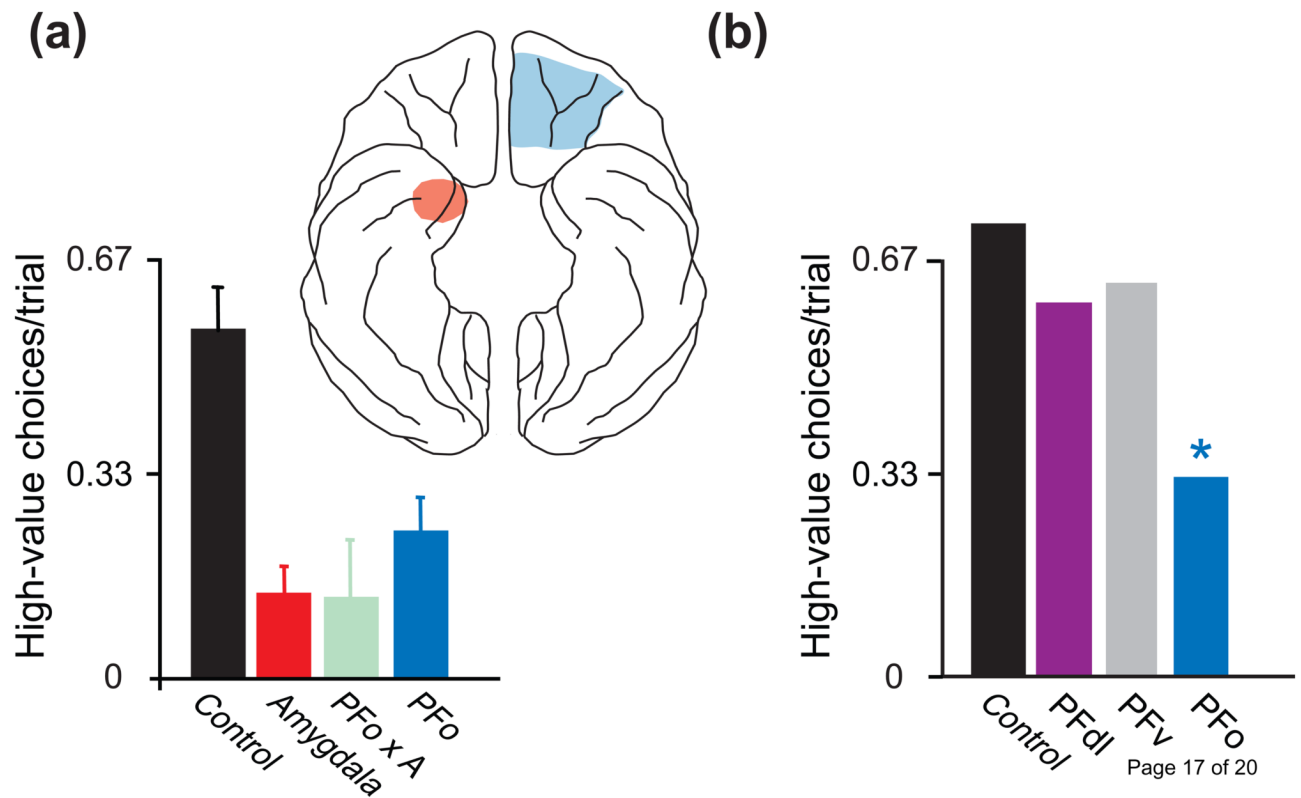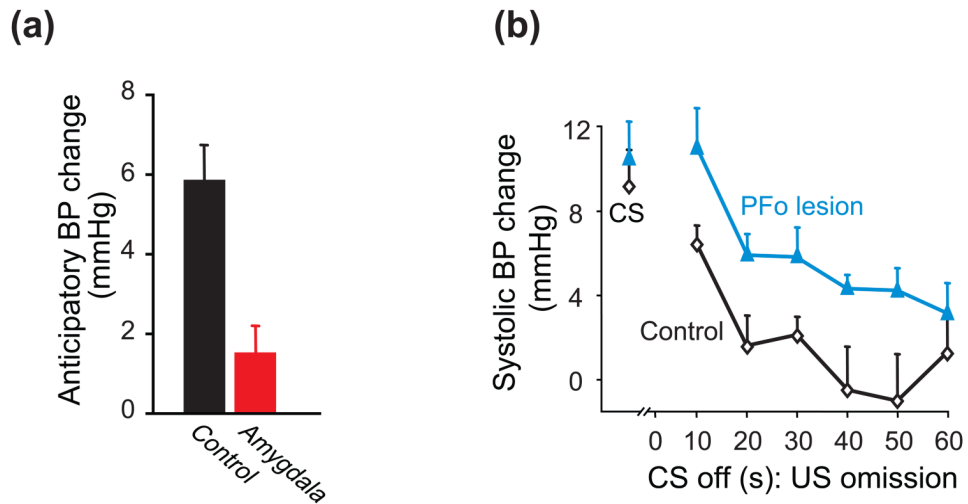
Figure 1.
Reinforcer devaluation. **(a)** Macaque monkeys chose between two objects, each associated with a different kind of food. Prior to the choice tests, one of the two foods had been devalued via selective satiation. Plot summarizes data from three different studies to show results from intact, control monkeys (pooled across studies) and monkeys with bilateral lesions of the amygdala [6], bilateral lesions of orbital prefrontal cortex (PFo), and crossed disconnection (illustrated in the inset) of the amygdala (A) from PFo (PFo × A). Each operated group differs significantly from controls. Error bars: SEM. **(b)** Results [7•,8•] from control monkeys and monkeys with bilateral lesions of the dorsolateral prefrontal cortex (area 46, PFdl), ventral prefrontal cortex (area 12, PFv), and PFo. *, significantly different from controls.
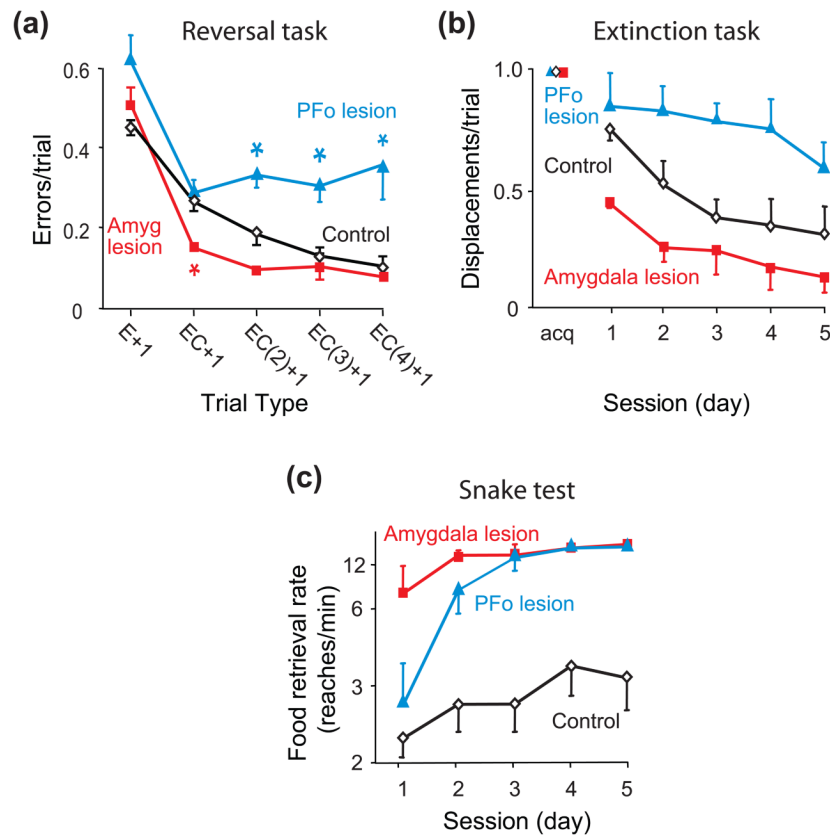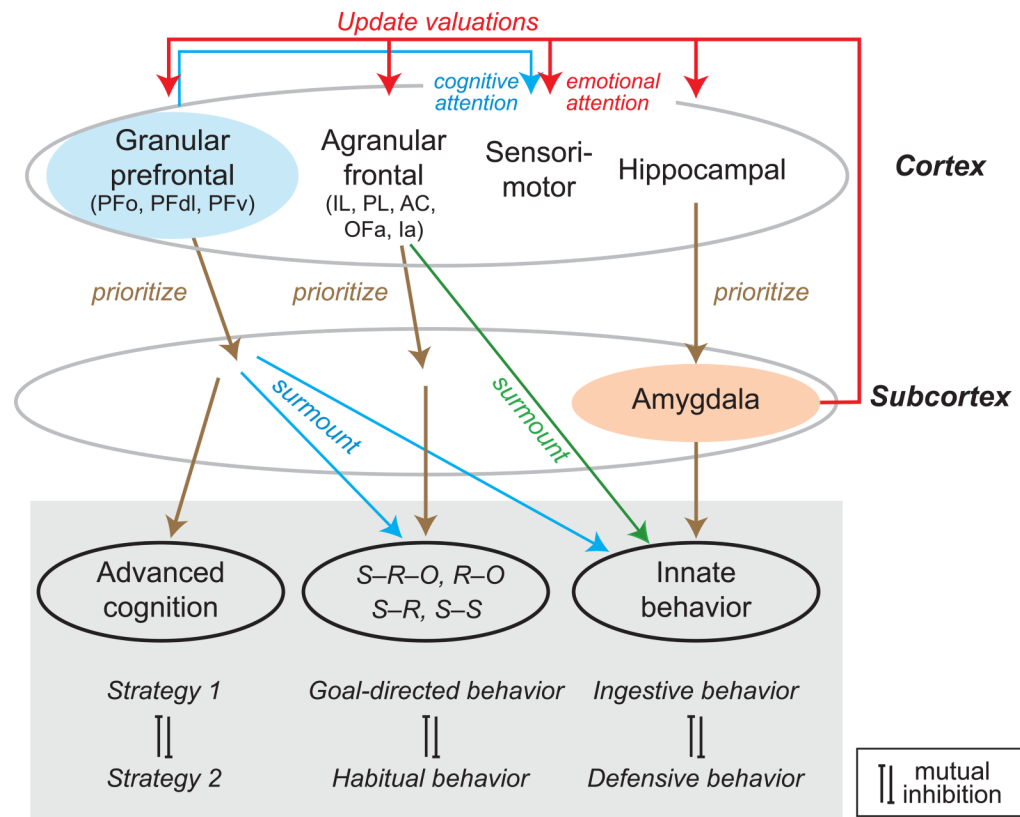
Figure 2.
Amygdala and PFo contributions to three behavioral tests in macaque monkeys. **(a)** Serial object-reversal learning [10••]. In this task, monkeys chose between two objects, and only one choice produced a food reward. The choice that did so changed periodically. Across a series of such reversals, monkeys with bilateral lesions of orbital prefrontal cortex (PFo) benefited less than controls after two, three or four correct (C) choices following an error (E) [EC(2)+1, EC(3)+1, and EC(4)+1 trial types, respectively]. Monkeys with bilateral amygdala (Amyg) lesions benefited more than controls when an error trial was followed by a single correct choice (EC+1 trial type). *, significantly different from controls. **(b)** Extinction. Monkeys first learned to displace a single object to obtain a food reward hidden underneath. After five consecutive days of consistently displacing the object to obtain food reward (acquisition, acq), object displacement failed to produce food over the next five days [12]. **(c)** Snake test. Food-retrieval rates when monkeys had to reach over a rubber snake to retrieve food [13]. Amygdala lesion group differed significantly from controls on all five sessions, whereas PFo group differed from controls on sessions 3–5 only. The fastest retrieval rates matched closely the times for reaching over neutral objects. Error bars: SEM.

(a)

(b)

Figure 3.
Pavlovian conditioning in marmoset monkeys. **(a)** Over several trials, marmosets saw a highly valued food for 20 s before being allowed to consume it. In intact monkeys, systolic blood pressure (BP) increased during the 20-s anticipatory phase; the amygdala lesion group displayed significantly lower BP relative to controls [15]. The Measure: millimeters of mercury (Hg). **(b)** First, marmosets learned that a tone (the conditioned stimulus, CS) indicated the availability of food (the unconditioned stimulus, US) during CS presentation. On a subsequent probe trial, the tone stopped (CS off) and the predicted food failed to appear (US omission). Points to left show BP during tone presentation; the series of points to the right show BP as a function of time after CS offset on the probe trial [16••]. Error bars: SEM.

Figure 4.
Scheme of interactions among cortical (top row) and subcortical (middle row) structures. According to this scheme, the granular prefrontal cortex prioritizes learned strategies, rules and other aspects of advanced cognition; the agranular frontal cortex prioritizes behaviors based on learned associations among stimuli (S), responses (R), and outcomes (O); and the hippocampal cortex and amygdala prioritize innate behaviors. The granular prefrontal cortex also implements advanced cognition by suppressing conditioned behaviors when warranted, and both the granular and agranular parts of frontal cortex suppress innate behaviors when warranted. Cortical-field abbreviations from left to right: PFo, PFdl and PFv, orbital, dorsolateral and ventral prefrontal cortex, respectively; IL, infralimbic cortex; PL, prelimbic cortex; AC, anterior cingulate cortex; OFa, agranular orbitofrontal cortex; Ia, agranular insular cortex.