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The primate amygdala combines information about space and value

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A stimulus predicting reinforcement can trigger emotional responses, such as arousal, and cognitive ones, such as increased attention toward the stimulus. Neuroscientists have long appreciated that the amygdala mediates spatially nonspecific emotional responses, but it remains unclear whether the amygdala links motivational and spatial representations. To test whether amygdala neurons encode spatial and motivational information, we presented reward-predictive cues in different spatial configurations to monkeys and assessed how these cues influenced spatial attention. Cue configuration and predicted reward magnitude modulated amygdala neural activity in a coordinated fashion. Moreover, fluctuations in activity were correlated with trial-to-trial variability in spatial attention. Thus, the amygdala integrates spatial and motivational information, which may influence the spatial allocation of cognitive resources. These results suggest that amygdala dysfunction may contribute to deficits in cognitive processes normally coordinated with emotional responses, such as the directing of attention toward the location of emotionally relevant stimuli.

Many aspects of emotional responses to stimuli are not spatially directed, such as freezing, autonomic reactivity or hormonal responses. However, stimuli that promote or threaten survival can also attract cognitive and behavioral resources, partly through their prioritization as a result of association with highly positive or negative outcomes[1]. For example, humans find negative images faster than they find emotionally neutral images[2], and they detect arousing words more readily[3]. Attention can also spread from arousing stimuli to nearby neutral ones[4,5] and to locations associated with emotionally relevant cues such as gaze direction[6] or learned associations with monetary outcomes[7].

The neural mechanisms linking humans' emotional world to spatial cognition remain poorly understood. The amygdala is important for learning, updating and maintaining the value of sensory events, and it mediates many aspects of nonspatial emotional responses[8]. Physiological work implicates the amygdala in the encoding of motivational significance, or value, of stimuli[9,10], but has not explored whether the amygdala is important for localizing motivationally significant stimuli. Indeed, the amygdala is heavily interconnected with the orbitofrontal cortex (OFC), whose neurons lack spatial selectivity[11], suggesting that information processed at the level of the amygdala may be largely nonspatial. However, data from patients with isolated amygdala damage raise the possibility that this structure's influence on behavioral responses involves an at-least indirect role in spatial processing[8]. For example, examinations of SM, a woman with bilateral amygdala lesions, show that she is impaired at recognizing fear in facial expressions because she does not look at the eyes[12]. This impairment disappears when she is instructed to fixate the eyes, suggesting that her impairment results from a failure to direct gaze and attention toward emotionally relevant parts of faces, a process that requires the linking of emotional recognition with spatial processing.

The amygdala could be involved in directing cognitive and behavioral resources toward stimuli in at least two ways. First, the amygdala may induce a vigilant or aroused state[13], perhaps enhancing global processing but leaving the representation of spatial information to other brain structures. Alternatively, the amygdala may register both the motivational significance and the location of stimuli, allowing it to influence cognitive and behavioral processes in space. To test these possibilities, we trained monkeys to perform a task in which reward-predictive visual cues were presented in different spatial configurations. We found that during task performance, individual amygdala neurons encoded the motivational significance of visual stimuli as well as their spatial configuration. Furthermore, neuronal activity was correlated with the trial-by-trial allocation of attention, suggesting that the representation of value and space in the amygdala influence the direction of spatial attention toward motivationally relevant stimuli.

RESULTS

Stimulus-outcome associations guide spatial attention

To evaluate how the spatial configuration of reward-predictive visual cues influences the allocation of cognitive resources, we trained three monkeys to perform one of two tasks (**Fig. 1a**). The basic structures of the tasks were the same in that cues associated with different amounts of reward briefly appeared near spatial locations in which monkeys subsequently performed a perceptual task. In both tasks, monkeys

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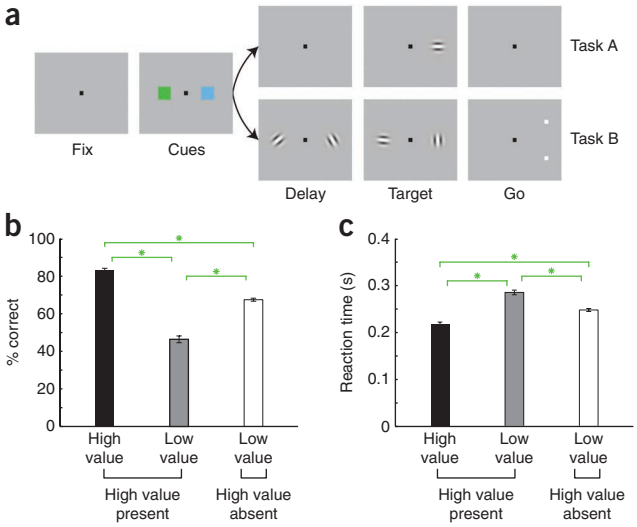

Figure 1 Motivational cues bias spatial attention. (**a**) Sequence of events in the two attention tasks. After monkeys achieved central fixation, two cues appeared at either side of the fixation point for 300 ms (task A) or 350 ms (task B). In task A (top), the cues were followed by a delay in which no peripheral stimuli were present. The brief appearance of a near threshold–oriented patch (50 ms) at one of the two locations served as the target, and the monkey correctly detected it by saccading to its location. In task B (bottom), two randomly oriented patches appeared on either side of the fixation point 250 ms after the cues were extinguished. At a random time point, the patches changed orientation simultaneously (in independent directions). A pair of choice targets was subsequently presented at one location, indicating which patch was the target, and the monkey judged whether the target at the indicated location was more vertical or horizontal. (**b**) Performance on high-value-present trials for targets appearing near the high-value cue (black bar) and the low-value cue (gray bar) and on high-value-absent trials (white bar). Performance is represented as the percentage of correct trials when the target appeared at the indicated location. (**c**) Reaction times for trials described in **b**. $^{*}P < 10^{-15}$, paired Wilcoxon; error bars, s.e.m. across sessions ($n = 126$ sessions).

initiated trials by fixating a central point and then held fixation during the brief presentation of two visual cues (appearing in opposite hemifields) and a subsequent delay. The delay terminated at a random time, at which a target stimulus appeared near one of the cue locations. The monkeys then reported the location of the target (task A; monkeys O and L) or the orientation of the patch revealed to be the target (task B; monkey C).

Each visual cue indicated how much liquid reward the monkey would receive for correct performance when the target appeared nearest the location of that cue; cues predicted either a high-value or a low-value outcome and were chosen from one of two cue sets, so that the effects related to the cue-outcome associations could be distinguished from those related to the physical characteristics of the cues. On each trial, we presented either two low-value cues (high-value-absent) or one high-value cue and one low-value cue (high-value-present; spatial configuration randomized with equal probability). We used performance and reaction time to assay the effects of the cues on behavior[14]. Because the target location was chosen randomly for each trial, we tabulated performance and reaction time for each location to determine how monkeys used cue-outcome associations to allocate cognitive resources. When the target appeared near the high-value cue on high-value-present trials, monkeys showed improved performance (**Fig. 1b**; 83% versus 46%, paired Wilcoxon, $P < 10^{-15}$) and faster reaction times (**Fig. 1c**; 218 ms versus 285 ms, paired Wilcoxon, $P < 10^{-15}$). On high-value-absent trials, performance was better and reaction times shorter than they were in high-value-present trials in which the target appeared near the low-value cue (**Fig. 1b**,**c**; paired Wilcoxon, $P < 10^{-15}$). Attention was roughly split between the two locations on high-value-absent trials (with hit rates of 69% and 66% for targets ipsilateral and contralateral to the recording location, respectively). We observed these behavioral effects in both tasks (**Supplementary Fig. 1**).

Amygdala neural activity reflects value and space

To determine whether the amygdala represents spatial as well as motivational information, we recorded the activity of 359 neurons from the amygdalae of three monkeys performing the two tasks (146 from left amygdala of monkey O; 59 from the left amygdala of monkey L; 154 from the right amygdala of monkey C; **Fig. 2**). Of these, 326 (91%) neurons were responsive during the tasks (see Online Methods), and we restricted all further analyses to this data set.

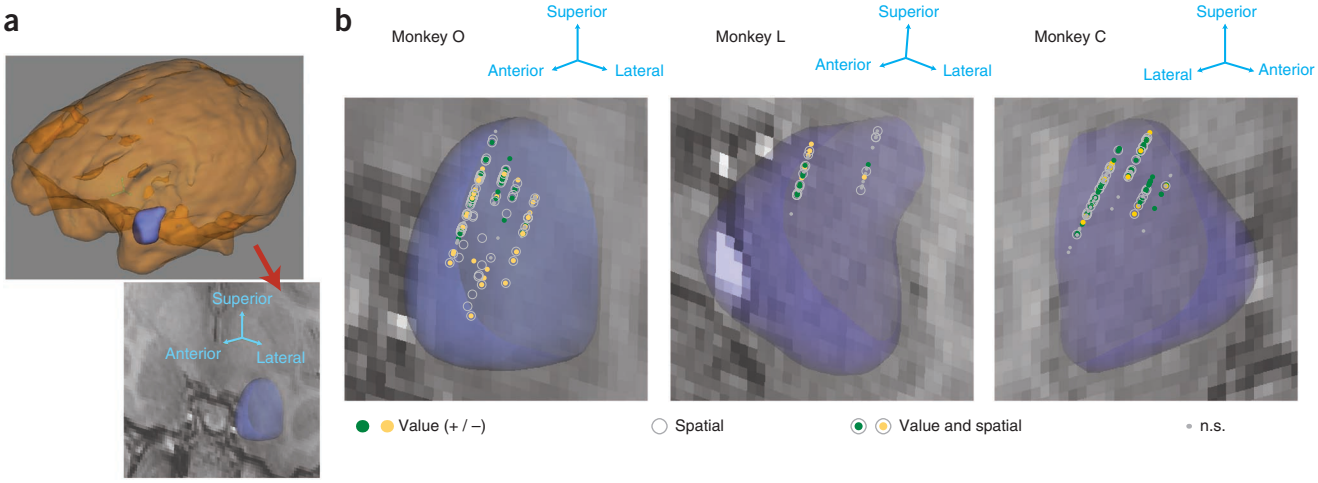

Figure 2 Reconstruction of recording locations. (**a**) Three-dimensional reconstruction of the whole brain and the amygdala of monkey O. (**b**) Three-dimensional reconstructions of the locations of recorded amygdala neurons, on a single coronal MRI (magnetic resonance imaging) slice from each monkey. Each coronal slice has been tilted to enable visualization of all electrode tracks. Arrows provide the orientation of the slice after tilting. Each circle represents the location of one neuron recorded during the task and the selectivity of that neuron (green, REW+; yellow, REW–); n.s., not significant.

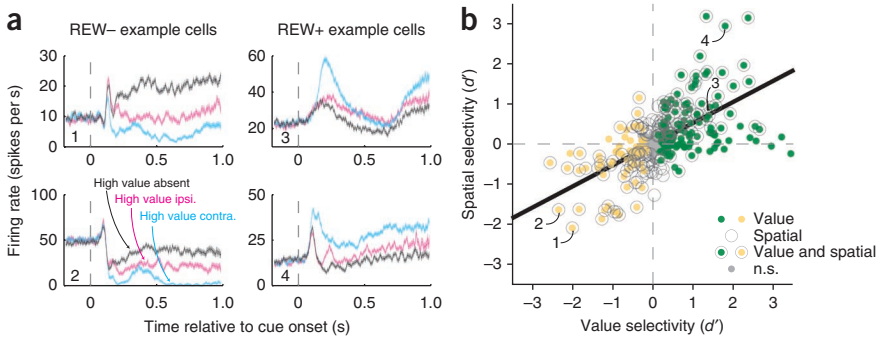

Figure 3 Amygdala neurons encode the value and spatial configuration of cues. (**a**) Peristimulus time histograms showing average firing rate plotted as a function of time relative to cue onset for four amygdala neurons (30-ms bins shifted by 2 ms; shading, s.e.m.). Value- and spatial-selectivity indices were significantly <0 (REW–; left) or >0 (REW+; right) for each example neuron ($P < 0.05$, bootstrap). (**b**) Scatter plot of spatial- versus value-selectivity indices for each individual neuron ($n = 326$ neurons). Value-selectivity indices >0 indicate higher activity when a high-value cue was present, and indices <0 indicate higher activity when the high-value cue was absent. Spatial-selectivity indices >0 indicate higher activity when the high-value cue was contralateral; values <0 indicate higher activity when the high-value cue was ipsilateral. Symbol style indicates the significance of selectivity for each neuron (green, REW+; yellow, REW–); black line represents the weighted least-squares regression fit ($\beta = 0.53$, $P < 10^{-6}$). One neuron with a value-selectivity index >3.5 was excluded from this plot and from the plots in **Figure 7a**. Numbers indicate data points corresponding to the example neurons in **a**. n.s., not significant.

We found that amygdala neural responses frequently encoded information about both the value and the spatial configuration of the cues (**Fig. 3a**). The activity of each example neuron was significantly (bootstrap, $P < 0.05$) dependent on the location of the high-value cue. Notably, the activity of these neurons was also modulated by the overall expected value of the cues. Consistent with prior studies[9,10], some neurons responded most strongly during high-value-absent trials (REW– neurons) and others during high-value-present trials (REW+ neurons; **Fig. 3a**).

The example neurons (**Fig. 3a**) are representative of the recorded population in two ways. First, expected reward and spatial configuration frequently had strong effects on neural responses. Second, there was a systematic relationship between value selectivity and spatial configuration selectivity. Neurons that signaled the presence of a high-value cue with an increase (or decrease) in activity also tended to respond more (or less) when the high-value cue was contralateral (**Supplementary Fig. 2**). We quantified these data by estimating selectivity indices (d') for each neuron on the basis of the firing rates 100–800 ms after cue onset. To calculate a spatial-selectivity index, we compared trials in which the high-value cue appeared contralaterally (high-value-contralateral) to those in which it appeared ipsilaterally (high-value-ipsilateral). We were surprised to find that 45% (148/326) of neurons were significantly modulated by spatial configuration (bootstrap, $P < 0.05$), of which 84 responded more and 64 responded less when the high-value cue was contralateral.

To calculate a value-selectivity index, we analyzed the same time window as for the spatial-selectivity index but compared high-value-present trials to high-value-absent trials. We identified many neurons whose activity significantly increased (REW+ neurons, $n = 122$ neurons) or decreased (REW– neurons, $n = 71$ neurons) when the overall expected value increased (bootstrap, $P < 0.05$).

If amygdala neurons indiscriminately combine spatial and value selectivity, these two measures would not be associated. This would be consistent with, for example, amygdala neurons combining value-related and space-related information in a random manner. Contrary to this hypothesis, we found a strong positive relationship between value- and spatial-selectivity indices (**Fig. 3b**; weighted least-squares regression and bootstrap, $\beta = 0.53$, $P < 10^{-6}$). This correlation was significant for the data from each task considered separately ($P < 10^{-4}$; **Supplementary Fig. 3**). Thus, individual amygdala neurons selectively combine information about space and value to signal the location of reward-predictive stimuli with both negative and positive excursions in firing rate. REW+ neurons signal the presence of a more valuable cue in contralateral visual space with increases in firing rate, whereas REW– neurons do the same with decreases in firing rate.

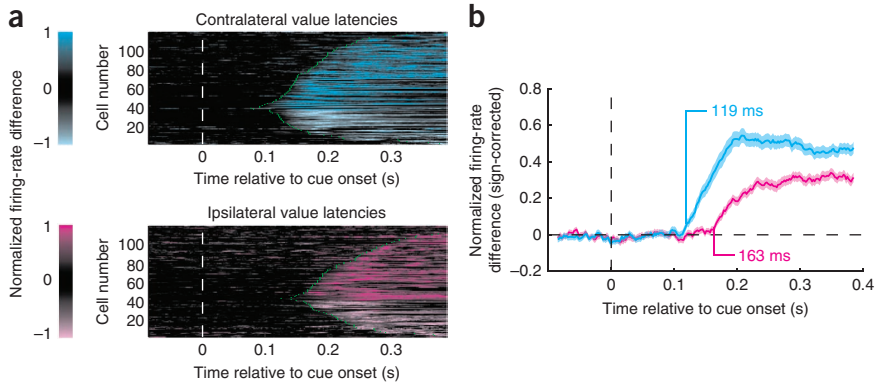

Figure 4 Latency of value discrimination by amygdala neurons depends on cue spatial configuration. (**a**) Time course of signals discriminating the value of cues. Color indicates the degree of differential firing on high-value-contralateral versus high-value-absent trials (top, cyan) and on high-value-ipsilateral versus high-value-absent trials (bottom, magenta). For each neuron and within each comparison, firing-rate differences within each condition were normalized by their maximum (unsigned) deviation from 0. Only cells with a measurable latency for each comparison were included; green circles indicate latency estimates (two contralateral and nine ipsilateral value latencies fall outside the plot). (**b**) Timing of value discrimination for the population of value selective neurons ($n = 193$ neurons). Average firing-rate differences (shading indicates s.e.m.) are plotted along with population value latencies for each comparison. For each neuron, we took the average of the two firing-rate difference curves, found the signed peak deviation from 0 (to enable averaging across REW– and REW+ neurons), and normalized the curve for each comparison by this value. This normalization maintains the difference in magnitude between the two comparisons.

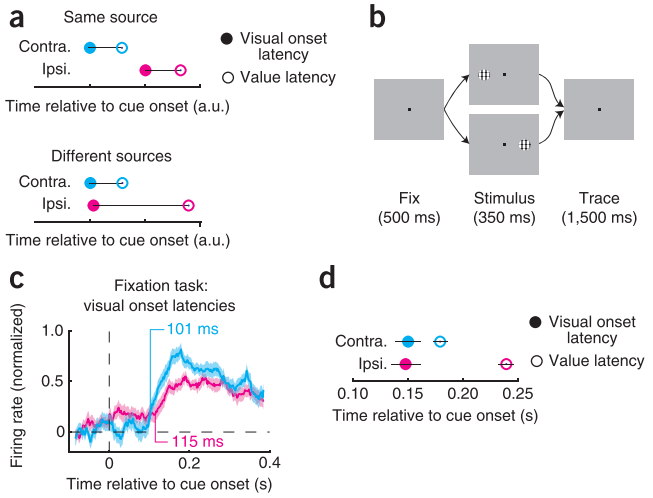

Figure 5 Latency of visual information is insensitive to spatial location. (**a**) Hypothetical latencies assuming that the delay in ipsilateral value information is already present in the feed-forward signal (delay derives from the same source) and that ipsilateral visual information and value information come from different sources (delay derives from different sources). Visual onset latencies and value latencies are illustrated as a function of time relative to cue onset. a.u., arbitrary units. (**b**) Fixation task. Monkeys were rewarded for maintaining fixation during the 350-ms cue presentation and for 1,000 ms thereafter; the reward magnitude was not dependent on the stimulus location. (**c**) Population visual onset latencies in the fixation task for contralateral and ipsilateral stimuli. Firing rates were normalized in the same manner as in **Figure 4b** (shading indicates s.e.m.). (**d**) Mean latencies for the set of cells for which the contralateral and ipsilateral visual onset latencies ($n = 19$ neurons) and/or the contralateral and ipsilateral value latencies ($n = 116$ neurons) could be estimated. Latencies are plotted as in **a**; horizontal bars indicate the s.e.m. for the distribution of single cell latencies.

Value-information timing depends on spatial configuration

The combined representation of space and value in the amygdala indicates that individual neurons encode information about the locations of high-value cues while also registering the values of contralateral and ipsilateral stimuli. It is possible that the spatial configuration selectivity we observed could result from weaker visual inputs representing the ipsilateral field, which may also carry value information or interact with value information arriving to the amygdala from other brain areas. To gain insight into these possibilities, we examined the latency with which amygdala neurons encode value in each visual hemifield.

First, we characterized how the location of a highly valued cue affects the time at which neurons begin to encode reward value. We determined when each neuron encoded the presence of a contralateral or ipsilateral high-value cue by comparing high-value-absent trials to trials in which a high-value cue appeared contralaterally or ipsilaterally (see Online Methods) and found that the value latency was shorter for contralateral high-value cues than for ipsilateral high-value cues for 97 (83%) of the 117 neurons for which we could estimate both latencies (**Fig. 4a**). The mean value latencies for contralateral and ipsilateral high-value cues were 177 ms and 240 ms, respectively, which differed significantly (Wilcoxon, $P < 10^{-11}$); this effect did not differ between REW– and REW+ neurons (Wilcoxon, $P = 0.73$) and was present in both tasks (**Supplementary Fig. 4a**,**b**). When we normalized and averaged activity across all value-modulated neurons ($n = 193$ neurons; **Fig. 4b**), we found that the presence of a contralateral high-value cue was signaled 44 ms earlier than an ipsilateral high-value cue (119 ms compared to 163 ms; bootstrap, $P = 0.001$). Thus, although amygdala neural activity is modulated by the value of contralateral and ipsilateral stimuli, this modulation starts at different times, suggesting the possibility of different neural sources for contralateral and ipsilateral value information.

If the observed differences in value latency could be explained by delays already present in the feed-forward inputs to the amygdala, we would expect to see a corresponding delay in the arrival of basic visual information from the ipsilateral visual field (**Fig. 5a**, top). Alternatively, ipsilateral value information may be even more delayed than basic ipsilateral visual information, indicating that ipsilateral value information is not simply inherited from a delayed feed-forward signal (**Fig. 5a**, bottom). To address this possibility, we recorded the activity of amygdala neurons ($n = 141$ neurons) during a fixation task (**Fig. 5b**) in which a single peripheral stimulus appeared either contralaterally or ipsilaterally (7° eccentricity). The fixation task allowed us to determine how visual onset latencies were influenced by spatial location, because a single stimulus, rather than two cues, appeared on every trial. Visual onset latencies for the population of visually responsive neurons ($n = 32$ neurons with significant response modulation after presentation of contralateral and ipsilateral stimuli) did not differ significantly across spatial locations (**Fig. 5c**; bootstrap, $P = 0.73$), nor did they differ for those neurons with measurable latencies at both stimulus locations ($n = 19$ neurons, paired Wilcoxon, $P = 0.8$). A direct comparison of individual value latency delays in the operant tasks ($n = 117$ neurons) with individual visual onset latency

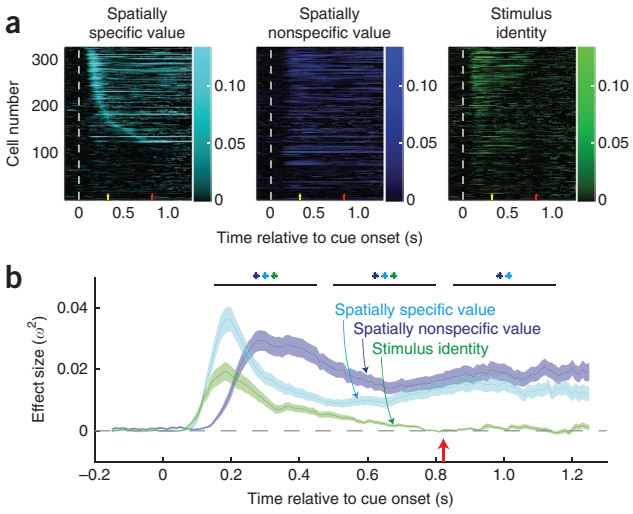

Figure 6 The encoding of space, value and stimulus identity by amygdala neurons evolves according to task demands. (**a**) Time course of amygdala signals representing spatially specific and nonspecific value, as well as stimulus identity, for individual value-selective neurons ($n = 193$ neurons). Color indicates effect size (ω^2) for each factor for individual neurons at times relative to cue onset (100-ms bins shifted by 10 ms). Neurons were sorted according to the onset of spatially specific value coding, and this ordering was the same in all three plots. The white dashed line indicates the time of cue onset; yellow and red arrows indicate the average time of cue offset and first target onset, respectively. (**b**) Time course of signals averaged over the population. Curves depict the mean and s.e.m. (shaded region) of ω^2 measures ($n = 326$ neurons). Black bars indicate the time bins used for statistical analysis, and asterisks indicate that the distribution of ω^2 for that time bin was significantly greater than during the baseline period ($P < 0.05$). Red arrow indicates the average time of first target onset.

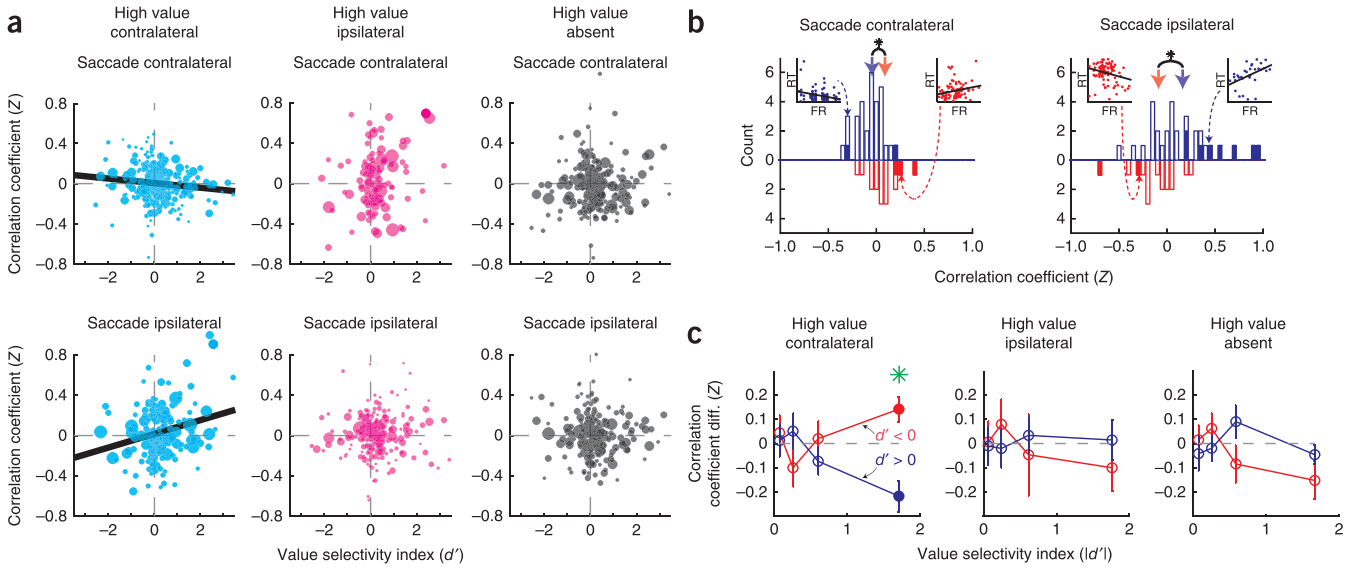

Figure 7 Trial-to-trial variations in firing rates are correlated with reaction time. (**a**) Relationship between value selectivity and correlations between firing rate and reaction time. Fisher *Z*-transformed correlation coefficients are plotted as a function of the value-selectivity indices for each trial type and saccade direction. Data point size indicates the reliability (inverse s.e.m.) of the correlation coefficient. Regression lines are plotted for instances in which a significant relationship was observed ($P < 0.05$, bootstrap). (**b**) Histograms of correlation coefficients on high-value contralateral trials for the quartile of neurons that was most value selective (on the basis of d' magnitude), split according to sign of selectivity (positive, $n = 31$ neurons, blue; negative, $n = 16$ neurons, red) and the direction of the saccade (contralateral, left; ipsilateral, right). Filled bars, individual neurons with correlation coefficients significantly different from 0 ($P < 0.05$); inset scatter plots, example cells with significant correlation coefficients (dashed arrows indicate their respective positions). The solid blue and red arrows indicate the mean of the distributions for positive-value and negative-value neurons, respectively; asterisks indicate that the mean correlation coefficients for these two groups were significantly different from each other ($P < 0.05$, bootstrap). (**c**) Correlation coefficient (*Z*) difference (Z_{contra}–Z_{ipsi}) plotted for cells grouped into quartiles according to $|d'|$ and then arranged according to sign of d'. Vertical bars, s.e.m. Blue and red solid circles, distributions significantly different from 0; green stars, distributions significantly different across groups (*t*-test, $P < 0.05$).

delays in the fixation task ($n = 19$ neurons) confirmed that the delay in value latencies was larger than that of visual onset latencies (**Fig. 5d**; Wilcoxon, $P = 0.0008$; this was true for both tasks) (**Supplementary Fig. 4c,d**). For 11 of the 68 neurons recorded in both fixation and operant tasks, we could compute all visual onset latencies and value latencies and found that the delay in ipsilateral value latencies was 63 ms longer than the delay in ipsilateral visual latencies (paired Wilcoxon, $P = 0.03$). Despite the dissociation of latencies between the tasks, we found that spatial location selectivity in the fixation task was a strong predictor of spatial configuration selectivity in the attention task (**Supplementary Fig. 5**). Thus, amygdala neurons integrate value information across the visual field, albeit with a longer delay than would be expected if this information were conveyed in a simple feed-forward manner.

Task-related signals have distinct time courses

If the conjoint spatial and value selectivity we observed is relevant in influencing behavior, it should be present not only while cues are presented but also when the monkey makes a discrimination (that is, when the target appears). We examined this by determining how different signal properties evolved during trials. For each neuron, we estimated the influence of the experimentally manipulated factors on neural firing rates using a multiple regression carried out in a sliding window relative to cue onset (**Fig. 6a**). In each window, we determined how neural activity was affected by three factors: the presence of a high-value cue, irrespective of spatial location (spatially nonspecific value), the presence of a high-value cue contralaterally (spatially specific value), and the cue set used (stimulus identity).

We focused our analysis on the time periods following cue presentation (cue period, 150–450 ms) and in the portions of the delay before (pre-target delay, 500–800 ms) and after (post-target delay, 850–1,150 ms) the earliest possible time of target onset (**Fig. 6b**). For both the cue period and pre-target delay, all three factors significantly influenced on firing rates (measured by ω^2 and compared to rates 300 ms before cue onset; bootstrap, $P < 0.005$). During the post-target delay, a different pattern emerged: signals for spatially specific and nonspecific value were maintained ($P < 10^{-4}$), but the encoding of stimulus identity disappeared ($P = 0.17$). This pattern was present in both tasks (**Supplementary Fig. 6**). This analysis reveals that both spatially specific and spatially nonspecific value signals are sustained into the time period during which the target could appear and could influence how the monkey performs the visual tasks.

Activity correlates with fluctuations in spatial attention

Attention waxes and wanes from trial to trial throughout an experimental session, and this presumably underlies some of the variability in behavioral measures, such as performance and reaction time, across trials[15]. If the combined representation of space and value in the amygdala influences the online guidance of spatial attention, trial-to-trial measures of amygdala activity and attentional allocation should covary. For example, consider an REW+ neuron, which responds more when the high-value cue is contralateral. Individual trials in which this neuron responds more than average should coincide with those trials in which the animal performs faster-than-average contralateral saccades (a classic measure of attention). This pattern would result in a negative correlation between neural activity and reaction time to targets in the contralateral field. Moreover,

a positive correlation for ipsilateral saccades (increased activity coinciding with slower saccades away from the contralateral side) would support a role in spatial attention. By contrast, correlations that are negative for both ipsilateral and contralateral saccades would suggest a function in nonspatial attention, such as alerting or vigilance, that could be modulated by changes in arousal level[13,15].

We examined the trial-by-trial relationship between saccadic reaction times and amygdala activity for the period ranging from 900 ms before to 100 ms after target onset, focusing on contralateral and ipsilateral saccade data separately. To determine whether the magnitude of correlation depends on cue value and/or spatial configuration, we analyzed each trial type separately, yielding a total of six conditions (3 trial types × 2 saccade directions). Finally, just as the sign of value selectivity predicted that of spatial configuration selectivity, we expected that it would also predict the sign of the correlation between firing rate and reaction time. Therefore, we used a linear regression to characterize the relationship between neurons' value selectivity (d') and their trial-by-trial relationship with reaction times (Fisher Z-transformed correlation coefficient). Consistent with spatial attention, but not alerting or vigilance, value selectivity had a negative relationship with contralateral correlation coefficients (bootstrap, $P = 0.0078$) and a positive relationship with ipsilateral correlation coefficients ($P = 0.0048$) when the high-value cue had appeared contralaterally (**Fig. 7a**). These relationships were not significant when the high-value cue was ipsilateral or absent, and the regression slopes on these trial types were significantly smaller than those observed on high-value-contralateral trials (analysis of covariance, $P < 0.005$ for each saccade direction). The relationship between firing rate and reaction time was robust and remained even after we accounted for differences in satiation and recent reinforcement-outcome history (**Supplementary Fig. 7**). In addition, the distance between the target and the fixational eye position after target onset (0–50 ms) did not explain these results; this distance was not correlated with reaction time ($P = 0.16$) and did not predict whether the monkey would perform the trial correctly (Wilcoxon, $P = 0.23$). Firing rates also predicted whether the monkey performed the trial correctly; however, differences in saccade behavior between 'hit' and 'miss' trials in the two tasks may have influenced these performance results (**Supplementary Fig. 8**).

The significant relationship between value selectivity and correlation coefficients on high-value-contralateral trials suggests that neurons with stronger value selectivity may have a stronger influence on attention. To examine this more closely, we split neurons into quartiles according to magnitude of value selectivity (absolute value of d') and then partitioned each group according to the sign of value selectivity. Focusing on the quartile of cells with the strongest value selectivity, we found that correlation coefficients differed significantly between neurons with positive selectivity ($d' > 0$) and neurons with negative selectivity ($d' < 0$) for both saccade directions (**Fig. 7b**; bootstrap, $P < 0.005$). Additionally, the distributions for ipsilateral and contralateral saccades were significantly different for positive-value neurons (bootstrap, $P = 0.001$; $\mu_{contra} = -0.04$; $\mu_{ipsi} = 0.16$), as were the distributions for negative-value neurons under the same comparison ($P = 0.004$; $\mu_{contra} = 0.09$, $\mu_{ipsi} = -0.09$). Thus the relationship between firing rate and reaction time differs depending on the locus of spatial attention as measured by reaction time. This finding was present in both operant tasks (**Supplementary Fig. 9**). Overall, these results support the notion that amygdala firing is correlated with spatial attention and not arousal-related processes.

The relationship between trial-by-trial firing rate of amygdala neurons and saccadic reaction time was not present for neurons that did not have strong value selectivity, and it was not present unless a high-value cue appeared in the contralateral field. We further assessed this by combining data across saccade directions and taking the difference in the Z-transformed correlation coefficients for each neuron (subtracting ipsilateral from contralateral), which, on the basis of the previous analysis, was negative for neurons with strong positive selectivity and positive for neurons with strong negative selectivity. For high-value-contralateral trials, correlation coefficient differences were significantly different from 0 (t-test, $P < 0.05$) only for neurons with the greatest value selectivity; the sign of this effect was opposite between the positive-value and negative-value groups (**Fig. 7c**). No significant effects were observed for any other groups of neurons in high-value-contralateral trials or for any group in high-value-ipsilateral or high-value-absent trials. Notably, neurons with the highest value selectivity also tended to have the widest spike waveforms (**Supplementary Fig. 10**), suggesting that these neurons may be projection neurons that influence attentional processing; this effect did not differ between neurons with positive value selectivity and those with negative value selectivity, nor did the overall distributions of waveform widths (Wilcoxon, $P = 0.66$). Taken together, these results suggest that the representation of space and value provided by the amygdala may have a function in spatial attention when highly valuable stimuli appear in the contralateral field and that this influence is mediated by the most value-selective amygdala neurons.

DISCUSSION

Motivationally salient stimuli trigger a range of cognitive and emotional responses that include spatially nonspecific processes, such as arousal or freezing induced by fear, and spatially specific responses, such as orienting attention. Although the amygdala has traditionally been understood to participate in spatially nonspecific responses, we found that amygdala neurons can combine information about both the spatial configuration of visual stimuli and the rewards predicted by stimuli. Moreover, we found that fluctuations in activity were correlated with fluctuations of spatial attention on a trial-by-trial basis. These results suggest that the amygdala not only participates in spatially nonspecific emotional responses but also may influence spatially specific cognitive processes, such as the allocation of enhanced cognitive resources to more valuable locations.

Amygdala neurons combine information about space and value such that activity changes in response to stimuli associated with greater rewards are associated with activity changes related to the spatial configuration of these stimuli. Previous studies showed that amygdala neural responses are sensitive to the reinforcement contingencies of conditioned stimuli presented over the fovea, with some neurons responding more strongly when a conditioned stimulus predicts a reward (rather than an aversive stimulus) and other neurons having the opposite response profile ('positive' and 'negative' value-coding neurons, respectively)[9,10]. We observed that positive (REW+) amygdala neurons, which responded more strongly when a highly valuable cue appeared, also responded most when this cue appeared contralaterally. By contrast, negative (REW–) amygdala neurons responded less to the presence of a highly valuable cue and also responded most weakly when this cue appeared contralaterally. The data suggest that although both ipsilaterally and contralaterally presented stimuli may drive amygdala neural responses, neurons can exhibit either positive or negative excursions in activity to signal the presence of a valuable cue in the contralateral field.

The discovery of a representation of space and value in the amygdala raises questions about the degree of spatial selectivity encoded

by amygdala neurons. In this study, we tested for spatial selectivity at the level of the visual hemifield. We observed that the onset latency of value information was strongly dependent on the locations of outcome-predictive stimuli, whereas visual response latencies were relatively insensitive to spatial location, suggesting that the spatial properties of amygdala neurons may have dynamic features that change depending on task demand. Indeed, when a monkey directed attention, a signal representing space and value was sustained in the amygdala throughout the trial, long after the visual cues were extinguished. Although spatial selectivity at the level of the hemifield during the fixation task predicts spatial selectivity during the operant tasks, our results indicate that it will be necessary to assess spatial properties in a variety of task contexts. The sheer number of trials required to map spatial properties in different tasks poses a substantial experimental challenge for the future. Our data suggest that the amygdala may at least be essential for quickly shifting attention to the left or right visual field on the basis of stimulus value.

How is this representation of space and value unique?

The response properties we describe suggest that the amygdala performs a function distinct from that of other brain areas that integrate information about space and value. Neurons encoding various aspects of rewarding and punishing outcomes have been discovered throughout the brain[16] and have been studied extensively through the use of single visual cues associated with different outcomes. Although these studies have shown how outcome-sensitive neurons may be relevant for computing the value associated with specific objects or actions[16], it is less clear how these neurons respond when there are multiple objects in the environment, particularly in situations in which resources must be divided and allocated.

Experiments in which two or more stimuli are presented simultaneously and associated with different values suggest that some brain areas combine space and value information to encode "action value"[17], the value associated with an available action. Two of the most studied brain structures in this regard are the lateral intraparietal area (LIP) and the dorsal striatum. During the performance of choice tasks, both the LIP and the dorsal striatum have been described as encoding the value of a choice in space[17,18]. Notably, neurons in these brain structures and those in the amygdala encode value differently. First, neither the LIP nor the dorsal striatum contains large populations of neurons (such as REW+ and REW– neurons) with sustained preferences for opposite reinforcement valences that are systematically related to spatial selectivity preference. Second, unlike our observations in the amygdala, neural responses in the LIP are inhibited according to the values associated with competing actions for targets appearing in the opposite hemifield[18,19]. Third, dorsal striatal neurons most frequently encode the value of a single action[20,21] or, similarly to neurons in the LIP, a quantity approximating the difference between the values of the two actions[22].

The encoding of action value in the LIP and the dorsal striatum often coincides with the locus of attention, or the preparation of an action whose endpoint is the locus of attention[23], but some data indicate that action value and attention can be dissociated[24]. Our results indicate that amygdala neurons do not represent only the locus of spatial attention; if they did, we would have observed intermediate neural responses for high-value-absent trials (in which attention is split approximately equally between the two hemifields) relative to trials in which the high-value cue appeared contralaterally or ipsilaterally (where attention is heavily biased toward one hemifield or the other). Instead, valuable stimuli in either hemifield modulate activity in the same direction for individual amygdala neurons, indicating that these neurons integrate value information across the visual field in addition to encoding information about the locus of spatial attention.

Another structure commonly investigated in relation to value is the OFC. The amygdala and the OFC are anatomically interconnected, and the physiological properties of neurons in the two areas are similar along many dimensions[9,10,25] (although there is some evidence that the dynamics of changing neural activity during learning differ between the two areas)[26]. However, when the OFC has been studied with tasks in which monkeys select one of two choice targets associated with different rules or values, neurons represent aspects of value without providing spatial information before selection[11]. Spatial coding also seems to be lacking in the ventral anterior cingulate cortex (vACC)[27], a brain area that is likely to participate in a functional network with the amygdala and the OFC, given its strong anatomical connectivity to both[28]. Thus, neurons in the OFC and vACC seem to be involved in computing the value of objects irrespective of where spatial attention and subsequent action are directed, which may be important in weighing possible outcomes and guiding economic choices. By contrast, the emergence of spatial properties in the amygdala raises the possibility that its function is distinct from those of the vACC and the OFC in modulating spatial cognition.

How is this representation of space and value created?

To allocate cognitive resources to valuable stimuli, information about 'where' and 'what' must converge with information about stimulus value. The amygdala is a potential site for this convergence; it receives direct inputs from the ventral visual stream[29], and single neurons in the amygdala encode stimulus value[9,10]. The source of spatial information in the amygdala is less clear. Direct projections to the amygdala from spatially selective areas such as the frontal eye fields or parietal cortex or the dorsal striatum are sparse or nonexistent in primates[29], suggesting that the dorsal visual pathway does not contribute directly to the spatial selectivity we observed. A pathway to the amygdala from the pulvinar has been proposed as source of subcortical inputs originating in the superior colliculus, which would allow rapid processing of emotional information that bypasses slower cortical pathways[30]. However, we suspect that this pathway does not have a special function in our experiments, as the visual onset latencies (>100 ms) we observed in the amygdala are consistent with visual information arriving through cortical pathways[31].

Another possibility is that neurons in the inferotemporal cortex, although not encoding value information[32,33], may provide enough spatial information for amygdala neurons to build the selectivity we observe[34]. However, the dissociation between the onset of visual information and value information in the amygdala suggests that these signals arise from different sources. Because the transfer of visual information between hemispheres is fast (~7–20 ms)[34,35], the relatively long delay (~50 ms) that we observed for ipsilateral value information suggests that it arises from a source other than the feed-forward visual pathway. One possibility is that value information is established in the contralateral amygdala and then passed to the ipsilateral amygdala, which would be an indirect transfer, as the amygdalae do not project to each other in primates[36]. Furthermore, a path through prefrontal cortices would probably be slow, as amygdala-prefrontal connections are exclusively ipsilateral[37], adding at least one additional synapse between the amygdalae.

Finally, it is also possible that the amygdala inherits its representation of space and value from other brain structures such as frontal cortical areas, many of which project to the amygdala with varying fiber density[28,29,37]. Unlike neurons in the OFC and the vACC, neurons in the dorsolateral (dl) and ventrolateral (vl) prefrontal cortex (PFC)

encode spatial information that can be enhanced by reward[38]. The vlPFC is part of a network important for orienting attention toward behaviorally relevant objects[39], and interactions with the amygdala may allow this network to orient attention on the basis of emotional significance, although the dlPFC and vlPFC project weakly to the amygdala[28]. In contrast, the amygdala is more interconnected with the dorsal ACC (dACC), and it was recently shown that a small subset of neurons in dACC and adjoining area 32 conjointly encode spatial attention and reward value[40]. However, the study in question did not report that representations of space and value were combined systematically, and the response latencies they measured were generally slower than those we observed in the amygdala, suggesting that the encoding of space and value information in the dACC may depend on inputs from the amygdala, which sends a relatively stronger return projection to the dACC[28].

How might the amygdala influence spatial attention?

Our data demonstrate that amygdala neurons can encode relevant locations in space defined by arbitrary stimulus-outcome associations. This combined representation of space and value could influence a number of cognitive processes, including decision-making based on option location and value as well as the allocation of attention. We considered two possible effects of the amygdala on attention. First, the amygdala might have a direct influence on spatial attention. In the sensory domain, when multiple stimuli are competing for limited processing resources, attention biases competition in favor of relevant stimuli[41], allowing the prioritization of specific spatial locations in the visual environment. Stimulus relevance may be determined by a wide variety of factors. In the simplest case—of orientation of the sensory receptors toward some stimuli and away from others—attention can operate in an exogenous (stimulus-driven, or 'bottom-up') or endogenous (goal-directed, or 'top-down') manner[39]. The former refers to reflexive processes by which organisms direct their sensory receptors toward abrupt or intense stimuli that violate expectations, and the latter refers to the typically voluntary orientation of attention toward an object or a location in space on the basis of an expectation about an environmental event. The association between rewarding outcomes and cues indicating spatial location is one such expectation[23], which we used to examine how the amygdala's processing of the cues is related to attention allocation.

A second means by which the amygdala might modulate attention involves the induction of a state of arousal that promotes vigilance[13]. 'Vigilance' refers to the ability to sustain attention for prolonged periods of time, which depends in part on an organism's state of arousal. Arousal is thought to be a spatially nonspecific way to allocate more processing resources, and the amygdala is thought to augment vigilance by modulating arousal[42,43] or to augment 'attention for learning', which is also spatially nonspecific[44,45].

If the amygdala influences spatial attention, the relationship between amygdala neural responses and quantitative measures of spatial attention would depend on the spatial location of the attended stimuli. Alternatively, if amygdala activity is related to spatially nonspecific arousal, then the relationship between amygdala neural responses and measures of spatial attention should have the same relationship regardless of the spatial location of the attended stimuli. Using reaction time as a measure of spatial attention, we found that for REW+ neurons, higher activity during the delay period predicted shorter reaction times to targets in the contralateral visual field and longer reaction times to targets in the ipsilateral field. For the same measure of spatial attention, we observed the opposite relationship for REW– neurons. Thus, our results suggest that the combined representation of space and value in the amygdala is related to the allocation of spatial attention, and the amygdala may therefore function in both spatially specific and nonspecific responses to motivational stimuli. Moreover, the presence of this correlation between neural activity and reaction time during the delay period, long after cues have disappeared from view, suggests that the amygdala represents cognitive information, not merely perceptual information. The representation of space and value could, in principle, also influence movement preparation, but amygdala neural responses related to saccadic execution have not been reported.

Amygdala activity representing space and value may not actually influence spatial attention, as signals from other brain structures representing spatial attention could modulate the observed representation of space and value in the amygdala. However, our suggestion that amygdala neural activity may itself influence the allocation of spatial attention may explain why electrical stimulation of the amygdala elicits orienting responses[46] similar to those observed during attentive states and why amygdala lesions result in conditioned orienting deficits[45]. We suspect that in our tasks the amygdala is not directly producing movements *per se*, because the monkeys were extensively trained to covertly attend while fixating. Instead, we believe that the amygdala could influence a number of brain systems involved with enhancing sensory processing. The amygdala could influence attention via direct projections to the cortex, including lower-level sensory areas[29], and to subcortical areas involved with attention, including the basal forebrain[45]. These connections could help explain the increased activation of the visual cortex to stimuli associated with reward or punishment[4,47] and the observation that amygdala damage reduces activation in response to fearful expressions in a hemisphere-specific manner[48]. As the local topography of the projections from the amygdala to the sensory cortices is unknown, it remains unclear whether amygdala enhancement of cortical processing occurs at the hemifield level, constrained by the ipsilateral bias in projections to the visual cortices[29], or in a more spatially specific manner.

We have shown that the amygdala links stimulus-outcome associations with their spatial relevance. Our results suggest that the amygdala may influence how a subject attends to valuable stimuli, with the two amygdalae competing to influence spatial attention when location is relevant and working in concert to increase vigilance when location is irrelevant or uncertain. Our findings may provide insights into neuropsychiatric disorders such as autism and schizophrenia, in which amygdala dysfunction is believed to underlie deficits in orienting attention according to emotionally relevant stimuli[49,50]. Thus the amygdala, long recognized as a crucial coordinator of emotion, may also perform a key function in representing emotional information in space, allowing it to influence spatially specific cognitive responses to the emotional world.

METHODS

Methods and any associated references are available in the online version of the paper.

Note: Supplementary information is available in the online version of the paper.

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AUTHOR CONTRIBUTIONS
B.L. initiated the project; C.J.P. and B.L. designed the experiments, collected the data and wrote the manuscript; C.J.P. analyzed data with assistance from B.L.; C.D.S. supervised and provided input about all aspects of the project and edited the manuscript.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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1. Lang, P.J. & Davis, M. Emotion, motivation, and the brain: reflex foundations in animal and human research. *Prog. Brain Res.* **156**, 3–29 (2006).
2. Ohman, A. & Wiens, S. in *Handbook of Affective Sciences* (eds. Davidson, R.J., Sherer, K.R. & Goldsmith, H.H.) Ch. 13 (Oxford University Press, 2003).
3. Anderson, A.K. Affective influences on the attentional dynamics supporting awareness. *J. Exp. Psychol. Gen.* **134**, 258–281 (2005).
4. Armony, J.L. & Dolan, R.J. Modulation of spatial attention by fear-conditioned stimuli: an event-related fMRI study. *Neuropsychologia* **40**, 817–826 (2002).
5. Phelps, E.A., Ling, S. & Carrasco, M. Emotion facilitates perception and potentiates the perceptual benefits of attention. *Psychol. Sci.* **17**, 292–299 (2006).
6. Klein, J.T., Shepherd, S.V. & Platt, M.L. Social attention and the brain. *Curr. Biol.* **19**, R958–R962 (2009).
7. Anderson, B.A., Laurent, P.A. & Yantis, S. Value-driven attentional capture. *Proc. Natl. Acad. Sci. USA* **108**, 10367–10371 (2011).
8. Phelps, E.A. & LeDoux, J.E. Contributions of the amygdala to emotion processing: from animal models to human behavior. *Neuron* **48**, 175–187 (2005).
9. Paton, J.J., Belova, M.A., Morrison, S.E. & Salzman, C.D. The primate amygdala represents the positive and negative value of visual stimuli during learning. *Nature* **439**, 865–870 (2006).
10. Belova, M.A., Paton, J.J. & Salzman, C.D. Moment-to-moment tracking of state value in the amygdala. *J. Neurosci.* **28**, 10023–10030 (2008).
11. Padoa-Schioppa, C. & Assad, J.A. Neurons in the orbitofrontal cortex encode economic value. *Nature* **441**, 223–226 (2006).
12. Adolphs, R. *et al.* A mechanism for impaired fear recognition after amygdala damage. *Nature* **433**, 68–72 (2005).
13. Davis, M. & Whalen, P.J. The amygdala: vigilance and emotion. *Mol. Psychiatry* **6**, 13–34 (2001).
14. Posner, M.I., Snyder, C.R. & Davidson, B.J. Attention and the detection of signals. *J. Exp. Psychol.* **109**, 160–174 (1980).
15. Parasuraman, R. & Davies, D.R. *Varieties of Attention* (Academic Press, 1984).
16. Schultz, W. Behavioral theories and the neurophysiology of reward. *Annu. Rev. Psychol.* **57**, 87–115 (2006).
17. Kable, J.W. & Glimcher, P.W. The neurobiology of decision: consensus and controversy. *Neuron* **63**, 733–745 (2009).
18. Sugrue, L.P., Corrado, G.S. & Newsome, W.T. Choosing the greater of two goods: neural currencies for valuation and decision making. *Nat. Rev. Neurosci.* **6**, 363–375 (2005).
19. Louie, K., Grattan, L.E. & Glimcher, P.W. Reward value-based gain control: divisive normalization in parietal cortex. *J. Neurosci.* **31**, 10627–10639 (2011).
20. Lau, B. & Glimcher, P.W. Value representations in the primate striatum during matching behavior. *Neuron* **58**, 451–463 (2008).
21. Samejima, K., Ueda, Y., Doya, K. & Kimura, M. Representation of action-specific reward values in the striatum. *Science* **310**, 1337–1340 (2005).
22. Cai, X., Kim, S. & Lee, D. Heterogeneous coding of temporally discounted values in the dorsal and ventral striatum during intertemporal choice. *Neuron* **69**, 170–182 (2011).
23. Maunsell, J.H. Neuronal representations of cognitive state: reward or attention? *Trends Cogn. Sci.* **8**, 261–265 (2004).
24. Peck, C.J., Jangraw, D.C., Suzuki, M., Efem, R. & Gottlieb, J. Reward modulates attention independently of action value in posterior parietal cortex. *J. Neurosci.* **29**, 11182–11191 (2009).
25. Morrison, S.E. & Salzman, C.D. The convergence of information about rewarding and aversive stimuli in single neurons. *J. Neurosci.* **29**, 11471–11483 (2009).
26. Morrison, S.E., Saez, A., Lau, B. & Salzman, C.D. Different time courses for learning-related changes in amygdala and orbitofrontal cortex. *Neuron* **71**, 1127–1140 (2011).
27. Cai, X. & Padoa-Schioppa, C. Neuronal encoding of subjective value in dorsal and ventral anterior cingulate cortex. *J. Neurosci.* **32**, 3791–3808 (2012).
28. Ghashghaei, H.T., Hilgetag, C.C. & Barbas, H. Sequence of information processing for emotions based on the anatomic dialogue between prefrontal cortex and amygdala. *Neuroimage* **34**, 905–923 (2007).
29. Freese, J.L. & Amaral, D.G. in *The Human Amygdala* (eds. Whalen, P.J. & Phelps, E.A.) Ch. 1, 3–42 (Guilford Press, 2009).
30. Tamietto, M. & de Gelder, B. Neural bases of the non-conscious perception of emotional signals. *Nat. Rev. Neurosci.* **11**, 697–709 (2010).
31. Pessoa, L. & Adolphs, R. Emotion processing and the amygdala: from a 'low road' to 'many roads' of evaluating biological significance. *Nat. Rev. Neurosci.* **11**, 773–783 (2010).
32. Rolls, E.T., Judge, S.J. & Sanghera, M.K. Activity of neurones in the inferotemporal cortex of the alert monkey. *Brain Res.* **130**, 229–238 (1977).
33. Liu, Z. & Richmond, B.J. Response differences in monkey TE and perirhinal cortex: stimulus association related to reward schedules. *J. Neurophysiol.* **83**, 1677–1692 (2000).
34. DiCarlo, J.J. & Maunsell, J.H. Anterior inferotemporal neurons of monkeys engaged in object recognition can be highly sensitive to object retinal position. *J. Neurophysiol.* **89**, 3264–3278 (2003).
35. Swadlow, H.A., Rosene, D.L. & Waxman, S.G. Characteristics of interhemispheric impulse conduction between prelunate gyri of the rhesus monkey. *Exp. Brain Res.* **33**, 455–467 (1978).
36. Demeter, S., Rosene, D.L. & Van Hoesen, G.W. Fields of origin and pathways of the interhemispheric commissures in the temporal lobe of macaques. *J. Comp. Neurol.* **302**, 29–53 (1990).
37. Ghashghaei, H.T. & Barbas, H. Pathways for emotion: interactions of prefrontal and anterior temporal pathways in the amygdala of the rhesus monkey. *Neuroscience* **115**, 1261–1279 (2002).
38. Kennerley, S.W. & Wallis, J.D. Reward-dependent modulation of working memory in lateral prefrontal cortex. *J. Neurosci.* **29**, 3259–3270 (2009).
39. Corbetta, M., Patel, G. & Shulman, G.L. The reorienting system of the human brain: from environment to theory of mind. *Neuron* **58**, 306–324 (2008).
40. Kaping, D., Vinck, M., Hutchison, R.M., Everling, S. & Womelsdorf, T. Specific contributions of ventromedial, anterior cingulate, and lateral prefrontal cortex for attentional selection and stimulus valuation. *PLoS Biol.* **9**, e1001224 (2011).
41. Desimone, R. & Duncan, J. Neural mechanisms of selective visual attention. *Annu. Rev. Neurosci.* **18**, 193–222 (1995).
42. Belova, M.A., Paton, J.J., Morrison, S.E. & Salzman, C.D. Expectation modulates neural responses to pleasant and aversive stimuli in primate amygdala. *Neuron* **55**, 970–984 (2007).
43. Kapp, B.S., Supple, W.F. Jr. & Whalen, P.J. Effects of electrical stimulation of the amygdaloid central nucleus on neocortical arousal in the rabbit. *Behav. Neurosci.* **108**, 81–93 (1994).
44. Roesch, M.R., Calu, D.J., Esber, G.R. & Schoenbaum, G. All that glitters dissociating attention and outcome expectancy from prediction errors signals. *J. Neurophysiol.* **104**, 587–595 (2010).
45. Holland, P.C. & Gallagher, M. Amygdala circuitry in attentional and representational processes. *Trends Cogn. Sci.* **3**, 65–73 (1999).
46. Ursin, H. & Kaada, B.R. Functional localization within the amygdaloid complex in the cat. *Electroencephalogr. Clin. Neurophysiol.* **12**, 1–20 (1960).
47. Padmala, S. & Pessoa, L. Affective learning enhances visual detection and responses in primary visual cortex. *J. Neurosci.* **28**, 6202–6210 (2008).
48. Vuilleumier, P., Richardson, M.P., Armony, J.L., Driver, J. & Dolan, R.J. Distant influences of amygdala lesion on visual cortical activation during emotional face processing. *Nat. Neurosci.* **7**, 1271–1278 (2004).
49. Baron-Cohen, S. *et al.* The amygdala theory of autism. *Neurosci. Biobehav. Rev.* **24**, 355–364 (2000).
50. Pinkham, A.E., Hopfinger, J.B., Pelphrey, K.A., Piven, J. & Penn, D.L. Neural bases for impaired social cognition in schizophrenia and autism spectrum disorders. *Schizophr. Res.* **99**, 164–175 (2008).

ONLINE METHODS

Animals and implantation. Three rhesus monkeys (*Macaca mulatta*, 8–13 kg) were used in these experiments. All experimental procedures complied with US National Institutes of Health guidelines and were approved by the Institutional Animal Care and Use Committees at the New York State Psychiatric Institute and Columbia University. Prior to training, each animal was surgically implanted with a plastic head post secured to the skull using ceramic bone screws. Surgery was conducted using aseptic techniques under isoflurane anesthesia, and analgesics and antibiotics were administered postsurgically. After behavioral training of monkeys, we acquired T1-weighted MRIs with fiducial markers fixed to the head post. In a second surgery, the MRI and fiducial markers were registered intra-surgically (Brainsight, Rogue Research, Quebec, Canada), allowing us to accurately implant a plastic recording chamber over the amygdala on the basis of the MRI for each monkey. We recorded the final position of the recording chambers and used these coordinates to the guide electrode placement during experiments. We logged the inferior/superior, anterior/posterior and medial/lateral position of each recorded neuron to generate a three-dimensional reconstruction using Brainsight software (**Fig. 2**). Although precise localization of all neurons to particular nuclei is not possible, using the MRIs and atlases we estimated that 297 neurons in our study were located in the basolateral complex and 29 neurons were located in the central nucleus.

Behavioral task. Monkeys were seated and head-restrained in darkened sound-attenuating booths during experiments and were operantly conditioned using liquid rewards. The monkeys performed one of two tasks designed to assess how reward expectations influenced attention. In both tasks, trials began with the monkeys fixating a central spot; the fixation window had a radius of 1.88 ± 0.03° in task A and 1.35 ± 0.03° in task B. In task A (monkeys L and O), a Gabor patch (sinusoidal grating windowed by a Gaussian) served as the target and then appeared at one of the two locations between 400 and 4,000 ms after cue offset (truncated exponential distribution) for 50 ms. The monkeys were required to saccade to the location of the target 100–600 ms after its onset. Because the interval during which the target could appear was long and the reaction time window relatively short, chance performance was about 23%. In task B (monkey C), the orientation of two Gabor patches changed at a random time 350–1,350 ms after their appearance (chosen from a truncated exponential distribution). Following a target duration of 80–120 ms (adjusted online according to the monkey's overall performance), the Gabor patches were then masked for 60 ms. Finally, two choice targets appeared around one of the two locations (4.2° away), indicating which Gabor patch was the target stimulus. The monkey was then required to saccade to one of the choice targets to indicate whether the target Gabor patch was more horizontal or more vertical (50% chance performance). The monkey had been trained to choose the counterclockwise target when the stimulus was more horizontal and the clockwise target when the stimulus was more vertical. In both tasks, trials were repeated when the monkeys made premature saccades. When the monkey failed to make a correct discrimination after the target appeared, the trial type was chosen at random on the next trial, just as we did when the monkey correctly performed the discrimination. Cues were colored rectangles (task A, 2.25 deg^2 at 7° eccentricity) or circles (Task B, 0.5° diameter at ~3° eccentricity), and we randomly interleaved two distinct sets of cues associated with the same outcomes.

We also trained two of the three monkeys (monkeys O and C) to perform a simple fixation task. After fixating a central point for 500 ms, a plaid grating (1.5° s.d. Gaussian window) appeared either to the left or right of the fixation point (7° eccentricity) for 350 ms. The monkeys were required to maintain fixation for an additional 1,000 ms to complete the trial and obtain a reward (delivered after an additional 500-ms delay).

Eye position was monitored using an infrared camera and digitized at 1,000 Hz (SR Research, Ontario, Canada). Reaction times were defined as the beginning of the saccade detected using an algorithm based on velocity and acceleration. Visual stimuli were generated using EXPO (Center for Neural Science, New York University) and were displayed on a CRT monitor positioned 61 cm away from the monkey.

Electrophysiology. Recordings from single amygdala neurons were made through a surgically implanted plastic cylinder affixed to the skull. Three to eight electrodes were individually lowered into the left (monkeys O and L) or right (monkey C) amygdala using a multiple-electrode microdrive (NaN Instruments, Nazareth, Israel). Extracellular activity was recorded using tungsten electrodes (2 MΩ impedance at 1,000 Hz; FHC Inc., Bowdoinham, ME). Analog signals were amplified, band-pass filtered (250–7,500 Hz) and digitized (30,000 Hz) for unit isolation (Blackrock Microsystems, Salt Lake City, Utah). Single units were isolated offline using waveform principal components (Plexon Offline Sorter, Plexon, Dallas, TX).

Data analysis. We used two-tailed statistical tests in all instances. For all bootstrap analyses, we randomly resampled with replacement to obtain replications with the same size as the original data set; this was repeated at least 10,000 times. Comparisons were significant if >97.5% of the bootstrap distribution fell on the same side of the null hypothesis or if the test statistics in one condition were greater than those in the other in >97.5% cases (both equivalent to a two-tailed test at $\alpha = 0.05$). Nonparametric Wilcoxon tests were performed on unpaired data (rank-sum test) unless specified otherwise (sign-rank test). We used *t*-tests only on data that were verified to be normal (Lilliefors test at $\alpha = 0.05$). Neurons were defined as task responsive if firing rates around the onset of the fixation point (100–600 ms), the cue (100–800 ms), the target (100–300 ms), or the reward (0–400 ms) differed significantly from baseline (1,000 ms before fixation-point onset; paired Wilcoxon, $P < 0.05$). For selectivity indices, we computed $d' = (\mu_1 - \mu_2) / \sqrt{((SS_1 + SS_2)/(df_1 + df_2))}$ where μ_X is the mean firing rate, SS_X is the sum of squares and df_X is degrees of freedom (number of trials–1) for each condition. Behavioral and neural data were similar across cue sets, so the data were combined except where noted.

Reaction-time correlation analysis. We calculated correlation coefficients between amygdala activity around target onset (900 ms before to 100 ms after) and saccadic reaction times. Before calculating each correlation coefficient, we subtracted the mean firing rate and reaction time for each cue set individually to ensure that any neural and/or behavioral differences between each cue set did not produce any across-group correlations. After mean subtraction, we calculated the correlation coefficients and applied the Fisher *Z*-transformation. To assess the relationship between value selectivity (d'; same values as in **Fig. 3b**) and the correlation coefficients, we used a least-squares regression weighted by the inverse standard errors of the *Z*-transformed correlation coefficients; significance was determined by a bootstrap analysis in which the set of cells for each resample was chosen randomly with replacement. Only correlation coefficients based on at least 15 trials were included for analysis; this resulted in a set of 274, 105 and 228 cells for contralateral saccades and 165, 215 and 208 cells for ipsilateral saccades (for high-value cue contralateral, ipsilateral and absent trials, respectively). We obtained similar results when we restricted the analysis of each trial type to the same set of cells ($n = 83$ neurons; those with 15 trials for each trial type and saccade direction).

Time-course analyses. We sought to determine how three factors influenced neural activity as a function of time: (i) the inclusion of a high-value cue irrespective of space (spatial nonspecific value); (ii) the inclusion of a high-value cue contralaterally (spatially specific value); and (iii) the use of the different cue sets (stimulus identity). For each factor, we computed the effect size, $\omega^2 = (SS_A - df_A \times MSE)/(SS + MSE)$, where SS_A is the across-group sum of squares for factor A, df_A is the degrees of freedom for factor A ($df_A = 1$ for all factors in our model), SS is the total sum of squares and MSE is the mean squared error of the model. The spatially nonspecific value component of this multifactor analysis differs from the d' value-selectivity index: a neuron that responds only on high-value contralateral trials would result in $\omega^2 > 0$ only for the spatial specific value signal but would have $d' > 0$ for both spatial selectivity and value selectivity (with the spatial-selectivity index roughly double in magnitude). The significance of values in each time bin was determined by comparison against those in the baseline interval (200 ms before cue onset; bootstrap). In comparison to the effect-size measure η^2 (proportion of total variance explained), ω^2 tends toward 0 when the explanatory power of the factor is weak and does not exhibit a positive bias for increasingly small sample sizes[51]. This was essential for analyzing cue-triggered responses because individual trials were truncated at the time of target onset, which occurred at a random time and resulted in progressively fewer trials available for analysis at increasingly later time times in the trial. Replotting **Figure 6** using the η^2 measure yields a similar result, but the values are biased upward at later time points.

Latency analyses. For all instances in which we computed value or visual onset latencies, we defined the latency as the first of 25 (population latencies) or 15 (individual neuron latencies) consecutive bins (30 ms bins slid by 2 ms) for which the comparison of interest was significant ($P < 0.05$). We used a bootstrap analysis to test for differences in population latencies.

For population value latencies, we first computed the difference in firing rates between high-value contralateral trials or high-value cue ipsilateral trials with firing rates on high-value-absent trials for each value-selective neuron ($n = 186$ neurons). Firing-rate differences were combined across REW– and REW+ by (i) subtracting any baseline firing-rate differences (500 ms before cue onset) and (ii) dividing by the signed peak deviation from 0 during the signal period. The peak deviation from 0 was based on the average of the two difference curves in order to illustrate the difference in their magnitude; the same results were obtained when the difference curves were normalized to reach the same asymptotic value. Neural discrimination in each post-cue time bin was tested against 0 (Wilcoxon).

We used an analogous analysis to determine visual onset latencies in the fixation task for the population of stimulus-responsive neurons (compare firing rates 100–300 ms after stimulus onset to 500 ms before stimulus onset; paired Wilcoxon, $P < 0.05$ for both locations). This included 32 neurons, of which 19 had excitatory responses, 11 had inhibitory responses and 2 had responses of opposite sign for the two cue locations. Again, we baseline subtracted, peak normalized and sign corrected the raw firing rates in order to obtain an average across neurons with excitatory and inhibitory responses; here, the peak response was based on the average of the responses to contralateral and ipsilateral stimuli. Visual onset latencies for contralateral and ipsilateral stimuli were estimated in the same way as for value latencies.

For individual visual onset latencies, we compared firing-rate distributions at each time bin (50–500 ms after cue onset) against the distribution of all baseline time bins (500 ms before cue onset; Wilcoxon). For individual value latencies, we compared firing-rate distribution on trials in which the high-value cue was contralateral or trials in which the high-value cue was ipsilateral with trials when the high-value cue was absent. The analyses of visual onset latencies and value latencies were limited to set of stimulus-responsive and value-selective neurons, respectively, as in the population analyses. We used a fairly stringent criterion to ensure that the measured latencies were accurate; as a result, value latencies and visual onset latencies could be computed for only a subset of value-selective ($n = 116/186$ value-selective neurons) and stimulus-responsive ($n = 19/32$ stimulus-responsive neurons) neurons, respectively.

51. Olejnik, S. & Algina, J. Generalized eta and omega squared statistics: measures of effect size for some common research designs. *Psychol. Methods* **8**, 434–447 (2003).

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