ORIGINAL ARTICLE

Neurons in the Human Left Amygdala Automatically Encode Subjective Value Irrespective of Task

F. Mormann^{1,2,3,†}, M. Bausch^{1,†}, S. Knieling¹ and I. Fried^{3,4}

¹Division of Epileptology, University of Bonn, 53105 Bonn, Germany, ²Computation and Neural Systems, California Institute of Technology, Pasadena, CA 91125, USA, ³Department of Neurosurgery and Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, Los Angeles, CA 90095, USA and ⁴Functional Neurosurgery Unit and Sackler Faculty of Medicine, Tel-Aviv Medical Center, Tel Aviv 64239, Israel

Address correspondence to Florian Mormann, Department of Epileptology, University of Bonn, Sigmund-Freud-Strasse 25, 53105 Bonn, Germany.
Email: florian.mormann@ukb.uni-bonn.de

[†]These authors contributed equally to this work.

Abstract

The amygdala plays an important role in the computation of internal reward signals. In animals it has been shown to enable a stimulus to indicate the current value of a reinforcer. However, the exact nature of the current value representations in humans remains unknown. Specifically, do neurons of the human amygdala represent current value signals only in tasks requiring valuation? We recorded from 406 neurons in the amygdala, orbitofrontal cortex, parahippocampal cortex, entorhinal cortex, and hippocampus of 6 neurosurgical patients while subjects repeatedly viewed 40 different pictures of sweet or salty “junk food” items in 2 different tasks. Neural activity during stimulus inspection in a valuation task reflected food preferences in the amygdala, orbitofrontal cortex, hippocampus, and entorhinal cortex. Notably, only left amygdala activity represented these food preferences even in a sweet-salty classification task. Valuation signals of the left amygdala thus appear to be stimulus-, not-task driven.

Key words: amygdala, electrophysiology, reward value, single units

Introduction

In pursuing their goals and satisfying biological needs, higher organisms constantly have to choose between alternative options. Potential rewards may vary in quality and type as well as in other dimensions such as amount and risk. A projection onto a common 1D scale of subjective value (also termed utility), however, would render them comparable (Glimcher 2009). Two behavioral implications following from such a projection of reward value, namely completeness (the probability of choosing b over a is determined by the probability of choosing a over b) and transitivity (preference of a over b and b over c implies preference of a over c) have indeed been observed in monkeys both behaviorally and electrophysiologically in dopamine neurons with prediction error signals reflecting integrated

subjective values (Lak et al. 2014). Brain regions that have been associated with reward processing include the midbrain, striatum, orbitofrontal cortex, and the amygdala. The amygdala has connections to all of these areas (McDonald 1998; Stefanacci and Amaral 2002). It receives inputs from sensory systems and interacts with error signals from midbrain dopamine neurons (Watabe-Uchida et al. 2012).

Single neuron activity in the amygdala has been reported to correspond to values of stimuli by themselves (Bermudez and Schultz 2010), to changing values during learning (Paton et al. 2006), to the expectation of outcomes (Belova et al. 2007), their timing (Bermudez et al. 2012), and in humans even to simple purchase decisions (Jenison et al. 2011). After amygdala lesions, human subjects show deficits affecting their daily life as well

as controlled decisions in gambling tasks, particularly under ambiguity and risk (Bechara et al. 1999; Brand et al. 2007). Such lesions have also been reported to abolish preference conditioning to abstract monochrome visual patterns through disguised pairings with food rewards under distraction in humans without reported awareness of such preference formation (Johnsrude et al. 2000). This raises the question whether the amygdala might represent current stimulus values automatically even when explicit valuation is not required by a task.

In this study we investigated whether neural firing in the amygdala might not only reflect current stimulus values when subjects are asked to report their food preference but even when they are asked to determine their sweet- or saltiness instead. Moreover, since the computation of current stimulus values seems to depend on the orbitofrontal cortex (Baxter et al. 2000; Walton et al. 2010; Rushworth et al. 2012; Clark et al. 2013), and the values themselves are thought to influence other regions including the hippocampus (Lee et al. 2012) or the entorhinal cortex (Paz et al. 2006), we investigated in which regions subjective values are represented.

Materials and Methods

Subjects and Recordings

All studies conformed to the guidelines of the Medical Institutional Review Board at the University of California, Los Angeles and the California Institute of Technology. Electrode locations were based exclusively on clinical criteria. Each electrode probe had 9 microwires protruding from its tip, 8 high-impedance recording channels (typically 200–400 k Ω), and one low-impedance reference with stripped insulation. The differential signal from the microwires was amplified using a 64-channel Neuralynx system (Bozeman, MT), filtered between 1 and 9000 Hz, and sampled at 28 kHz. Spike detection and sorting was performed after band pass filtering the signals between 300 and 3000 Hz using Wave_clus (Quiroga et al. 2004). Sorted units were classified as single units, multiunits, or artifacts based on spike shape and variance, ratio between spike peak value and noise level, the interspike interval distribution of each cluster, and presence of a refractory period for the single units. We recorded from 6 patients with pharmacologically intractable epilepsy (all right handed; 2 males; 22–43 years old), implanted with intracranial electrodes to localize the seizure focus for possible surgical resection (Fried et al. 1997). The locations of seizure foci were symmetric across subjects (1 left, 1 right, 3 bilateral, and 1 unclear). Our dataset consisted of 11 experimental sessions during which we recorded from microwires in the amygdala (A), hippocampus (H), entorhinal cortex (EC), parahippocampal cortex (PHC), and orbitofrontal cortex (OF). Microwire bundles were localized using a postimplantation CT scan coregistered with a preimplantation MRI scan, and normalized to Montreal Neurological Institute space. Figure 1 shows an exemplary localization plot of the amygdala (for other regions see Supplementary Fig. S2). The number of sessions per patient ranged from 1 to 3. Each session lasted approximately 20 min.

Experimental Protocol

Before the experiment, subjects were presented with a suitcase containing 40 different “junk” food items (34 sweet, 6 salty foods) for 5 min in order to familiarize them with the real-life versions of the stimulus set. Junk food items consisted of various snacks with plenty of calories, salt, sugars, or fats. During

Figure 1. Localization of microwire bundles with and without value-encoding neurons in the amygdala. The tips of the microwire bundles were localized using a postimplantation CT scan coregistered with a preimplantation MRI scan, and normalized to Montreal Neurological Institute space. Recording sites (i.e., location of bundle tips) projected onto a coronal (upper left), sagittal (upper right), and axial (bottom left) section of the MNI ICBM brain for all 6 subjects. All 11 recording sites were individually verified to be located in the amygdala. Value-encoding bundles were defined as bundles with a number of valuation units exceeding chance in a binomial test.

the experiment, subjects were sitting in bed, facing a laptop screen on which pictures of these junk food items were displayed on a black background, covering about 15° of visual angle, and presented for 3 s in pseudorandom order. This procedure was repeated 5 more times for a total of 6 runs. During the first 3 runs, subjects had to indicate how much they would like to eat the displayed item at that moment by pressing a number between 1 and 4 after image offset (valuation condition, Fig. 2A). During the second 3 runs, instead of indicating their preference, subjects had to decide whether the item displayed was sweet or salty by pressing the up or down button, respectively (sweet–salty condition, Fig. 2B).

Statistical Analysis

A) Behavior

Test–retest reliability of repeated stimulus ratings within sessions and inter-rater reliability of mean stimulus ratings across sessions were assessed by Kendall’s coefficient of concordance W (Kendall and Smith 1939). Kendall’s W is a measure of the consistency of ordinal ratings and is linearly related to the mean of Spearman’s rank correlation coefficients between all pairs of presentations. Test–retest reliability of repeated sweet–saltiness classifications and inter-rater reliability of most frequent image classifications were quantified accordingly by Fleiss’ kappa.

B) Unit-Analyses

Spearman correlations between firing rates and ratings from the valuation condition were performed for each unit using an alpha-level of 0.05. All firing rates were computed over a time window between 0 and 3000 ms after image onset. In order to account for multiple comparisons, we assessed the probability

Figure 2. Experimental paradigm. Pictures of 40 different food items were presented. The experiment was divided into 2 parts, each containing 3 presentation runs of the 40 pictures. (A) In the first part, subjects had to indicate how much they would like to eat the displayed item at the moment by pressing a number from 1 to 4 (valuation condition). (B) In the second part of the experiment, instead of indicating their preference, subjects had to decide whether the item displayed was sweet or salty by pressing the up or down button (sweet-salty condition).

of obtaining the observed number of significant correlations with a binomial test using an expected false positive probability of $P = 0.05$, identical to the alpha-level of the Spearman correlations. Furthermore, to account for nonindependence of neural activity and multiple ratings of the same picture, we performed 2 permutation tests with 10 000 permutations of either all 120 presentations (trial permutation test) or the 40 picture labels (picture permutation test) for both conditions. Each permutation thus affected correlations of all neurons from all sessions equally. The P -value was defined as the proportion of permutations whose regional number of false positive correlations was greater than or equal to the observed number of significant neurons in the respective region. All correlational analyses of the sweet-salty condition when subjects were not rating the items were performed using the last reported rating for each item from the valuation condition as the most likely estimate for true subjective values (Fig. 4).

To assess whether value representations are task-invariant we tested for positive Spearman correlations between

Figure 3. Single neuron in the left amygdala showing a significant rank correlation between liking ratings (from 1 to 4) and firing rates during the 3000 ms for which food items were presented in the first half of the experiment (Spearman's $\rho = 0.357$; $P < 0.0001$). Raster-plots, peristimulus time histograms, and lower boxplot depict firing rates as a function of ratings. The inset shows a density plot of the 1377 action potentials fired by this neuron during the experimental session.

differences in mean firing rate for high (3 or 4) versus low (1 or 2) rated images during the valuation condition with corresponding firing differences during the sweet-salty condition (Fig. 5).

In control analyses we assessed the number of units representing sweet- or saltiness during the sweet-salty condition by a Wilcoxon test performed at an identical alpha-level of 0.05. Moreover, we also evaluated the task invariance of potential sweet-salty representations by computing direct Spearman correlations between differences in mean firing rate for items labeled as sweet versus salty from both conditions for all regions.

To account for multiple comparisons of different sites, all reported P -values were corrected using the Holm-Bonferroni method across regions, unless explicitly stated otherwise.

Results

During 11 experimental sessions we recorded from 406 neurons in 6 subjects with pharmacologically intractable epilepsy, implanted with chronic electrodes to localize the seizure focus for possible surgical resection. We report data from microelectrode recordings in the amygdala, parahippocampal cortex, entorhinal cortex, hippocampus, and orbitofrontal cortex. The complete dataset included 406 units (271 multiunits/135 single units): amygdala 172 units, hippocampus 75 units, entorhinal cortex 61 units, parahippocampal cortex 42 units, orbitofrontal cortex 56 units. In the valuation condition, each food item was

Figure 4. Numbers of neurons showing a correlation between firing rates and liking ratings during the valuation condition. (A) Number of neurons of all 5 sites. Neurons whose firing rates showed a significant Spearman correlation with ratings given in the valuation condition ($\alpha = 0.05$) are colored in red, remaining neurons are colored in blue. Results from binomial tests as well as picture and trial permutation tests are indicated by asterisks (B) Same as A, but for separate hemispheres. *** $P < 0.001$; ** $P < 0.01$; * $P < 0.05$; Holm-Bonferroni correction for multiple comparisons.

rated at 3 different times according to current preference (Fig. 2). In the sweet-salty condition the sweet- or saltiness of each depicted food items was reported 3 times also. Valuation ratings were highly consistent across 3 repeated stimulus presentations (mean Kendall's $W = 0.867 \pm 0.101$ SD) but rather inconsistent across sessions (mean Kendall's $W = 0.239$). Sweet-saltiness classifications were highly consistent both across presentations (Fleiss $\kappa = 0.875 \pm 0.161$ SD) and across sessions (Fleiss $\kappa = 0.960$). Only 2 of 11 sessions exhibited a significant difference in valuation ratings for sweet versus salty items as quantified by a Wilcoxon rank-sum test with Holm-Bonferroni correction. Moreover, mean valuation ratings for sweet versus salty items did not differ systematically across all 11 sessions in a Wilcoxon signed rank test ($P = 0.8135$).

For the analysis of neuronal activity, we first screened for neurons in our dataset whose activity during the repeated picture presentations of the food items in the valuation condition correlated significantly with patients' ratings (Spearman's rank correlation; Fig. 3). A significant correlation was found for 13% of the entire set of neurons ($P < 10^{-8}$, binomial test), as well as for the subsets of neurons in amygdala, hippocampus, entorhinal cortex, and orbitofrontal cortex, but not in parahippocampal cortex (A: $P = 0.0021$ [20/172]**, H: $P = 0.0096$ [10/75]**, EC: $P = 0.0096$ [9/61]**, OF: $P = 0.0021$ [10/56]**, PHC: $P = 0.2729$ [4/42]).

Could these correlations merely be a result of stereotypical neural responses to particular visual stimuli regardless of their value? Invariant neural responses to individual stimuli have been reported in the medial temporal lobe (Quiroga et al. 2005). This question was addressed by our permutation tests. The same permutations of either the picture labels or the entire trial order across 3 presentation runs were applied to all neurons. Thus stereotypic neural activity, similar ratings of the identical food items, and nonindependence of neural activity

was reflected by the regional number of false positive correlations and bootstrap P -values. Both the trial permutation test (A: $P = 0.0045^{**}$, H: $P = 0.0168^{*}$, EC: $P = 0.0406^{*}$, OF: $P = 0.0045^{**}$, PHC: $P = 0.1683$) as well as the picture permutation test (A: $P = 0.0380^{*}$, H: $P = 0.0380^{*}$, EC: $P = 0.0724$, OF: $P = 0.0110^{*}$, PHC: $P = 0.3397$) confirmed significant numbers of value-encoding neurons in the amygdala, hippocampus and orbitofrontal cortex. The entorhinal cortex reached significance in one of the 2 permutation tests (Fig. 4).

Separate analysis of each hemisphere revealed significant numbers of rating-correlated neurons in left amygdala, right hippocampus, right entorhinal cortex and right orbitofrontal cortex (binomial test: LA: $P = 0.0003$ [18/120]***, RH: $P = 0.0263$ (6/30)*, REC: $P = 0.0274$ [7/41]*, ROF: $P = 0.0095$ [7/33]**, trial permutation test: LA: $P = 0.002^{**}$, RH: $P = 0.0408^{*}$, REC: $P = 0.2023$, ROF: $P = 0.0126^{*}$; picture permutation test: LA: $P = 0.0180^{*}$, RH: $P = 0.0544$, REC: $P = 0.3269$, ROF: $P = 0.0252^{*}$). Left amygdala and right orbitofrontal cortex remained significant in both permutation tests, right hippocampus in the trial permutation test only, and right entorhinal cortex in neither of them. The proportion of value neurons varied from approximately 5% in the right amygdala, to 15% in the left amygdala and 20% in the right orbitofrontal cortex.

To assess task independence of correlations, we calculated positive Spearman correlations between differences in mean firing rate for high (3 and 4) versus low (1 and 2) rated images during the valuation condition and corresponding mean firing differences during the sweet-salty condition. A significant effect was found only in left amygdala ($\rho = 0.338$, $P < 10^{-4}$). The second largest direct correlation was present in ROF, but did not reach significance ($\rho = 0.278$, $P = 0.059$). All other effect sizes were smaller than $\rho = 0.221$ with P -values greater than 0.087 (Fig. 5).

Figure 5. Differences in mean firing rate for high (3 and 4) versus low (1 and 2) rated images during the valuation condition plotted against corresponding differences in firing rates during the sweet-salty condition. Most recent image ratings were used as the most likely value estimate for each food item. Neurons with a significant correlation in the valuation condition are shown in red. Diagonal dotted black lines indicate the hypothetical case of identical firing rate differences in both conditions. Regional positive Spearman correlations of all rate differences (both unit types) between both conditions were significant only in the left amygdala. P-values and effect sizes of direct Spearman correlations are shown in the lower right corner of each subplot. Alpha-levels were Holm-Bonferroni corrected for multiple comparisons.

Figure 6 shows trial-by-trial spiking activity of 3 exemplary units in left amygdala with raster plots for different ratings under both experimental conditions, showing various degrees of task-invariance. In control analyses we determined the number of units representing sweetness or saltiness. Wilcoxon comparisons of median firing rates during the sweet-salty condition revealed a significant number of sweet-salty selective units in amygdala and orbitofrontal cortex (Supplementary Fig. S1; A: $P = 0.0245^*$, H: $P = 0.8009$, EC: $P = 0.7465$, OF: $P = 0.0021^{**}$, PHC: $P = 0.1718$). In a hemisphere-wise analysis, only left orbitofrontal cortex continued to show a significant effect (LA: $P = 0.0647$, LOF: $P = 0.0009^{***}$).

In contrast to task-invariant representations of value, none of the brain regions exhibited a significant direct Spearman correlation between differences in mean firing rate for items labeled as sweet versus salty from both conditions (all corrected P-values greater than 0.23).

Discussion

We found significant proportions of neurons in left amygdala, right hippocampus, right entorhinal cortex, and right

orbitofrontal cortex whose activity during subjects' valuation of visual food stimuli was correlated with reported subjective values (Fig. 4). Our data thus points to a representation of subjective values in human orbitofrontal cortex as well as amygdala, and implicates 2 new regions for further investigation, namely, hippocampus and entorhinal cortex, in humans. Of all regions analyzed, only units in left amygdala represented liking ratings not only when subjects were explicitly valuating the food items, but even when they determined their sweet- or saltiness instead, as measured by correlations of differences of mean firing rate for high (3 and 4) versus low (1 and 2) rated images under both conditions (Fig. 5). Although we cannot exclude the possibility of invariant value representations in other brain regions that were not detected in this study due to lower sample sizes, particularly in right orbitofrontal cortex with the second largest effect size ($\rho = 0.278$), left amygdala clearly exhibited the strongest effect size of all regions analyzed ($\rho = 0.338$). Our findings suggest that single unit activity of the left amygdala represents value information upon the sight of a visual stimulus irrespective of task and explicit valuation requirements (Fig. 6). Additionally, a significant amount of units distinguished sweet- or saltiness in amygdala and orbitofrontal cortex. These units,

Figure 6. Raster plots of 3 left amygdala neurons with a significant correlation in the valuation condition for different ratings and experimental conditions (valuation/sweet-salty). For the sweet-salty condition, the last reported ratings from the valuation condition were used for each item as the most likely estimate for true subjective value. All raster plots are sorted by stimuli in descending order of mean firing in the valuation condition (i.e., not in chronological order). Note the varying degrees of similarity of firing patterns under both conditions. (A) Same neuron as in Figure 3 with relatively weak correlation in the sweet-salty condition (valuation $\rho = 0.3568$, sweet-salty $\rho = 0.1007$). (B) Neuron with intermediate correlation in the sweet-salty condition (valuation $\rho = 0.2294$, sweet-salty $\rho = 0.1805$). (C) Neuron with strong (negative) correlation in the sweet-salty condition (valuation $\rho = -0.2622$, sweet-salty $\rho = -0.4145$).

by contrast, did not represent sweet- or saltiness during the valuation part arguing against task-invariance due to idiosyncratic stimulus response patterns.

Our subjects were epilepsy patients. While we do not expect changes associated with epilepsy to lead to spurious value correlations, we cannot exclude the possibility of detecting fewer valuation neurons in some of the investigated brain regions due to loss of neurons or function in diseased tissue. However, sides of epileptic foci were symmetric across our patients and units were distributed rather evenly among them, particularly in the amygdala. Moreover, there is growing evidence that the inclusion of units located in the same brain hemisphere as the epileptic focus does not systematically distort results of single unit studies (Mormann et al. 2008). Previous single unit studies have likewise reported asymmetrical findings that could not be attributed to epilepsy (Mormann et al. 2011).

While other variables, such as judgment effort and attention or confidence and biological significance can be correlated with subjective value, these variables tend to be correlated with subjective value only for preferred or only for disliked items, not across the entire spectrum of possible subjective values. We did not explicitly measure negative values of food items in our experiment, nor did we quantify a level of indifference to food items. However, we selected a diverse set of 40 food items and subjective values for these items varied across sessions as evidenced by a low inter-rater reliability (Kendall's W of 0.239). Therefore, we assume the spectrum of possible subjective values was sampled sufficiently to primarily detect a value relationship.

Stable task-invariant valuation responses in the left amygdala are in accordance with macaque valuation research. In macaques amygdala reward neurons show much less evidence of rapid, one-trial visual discrimination reversal (Sanghera et al. 1979; Wilson and Rolls 1993, 2005), and of decreased firing after feeding to satiety (Sanghera et al. 1979; Rolls et al. 1989). They do not seem to update by learning or by reward devaluation to correctly influence choice (Rolls 2014, 2016). In contrast valuation neurons in the orbitofrontal cortex reflect current reward value both in one-trial visual discrimination reversal (Thorpe et al. 1983; Rolls et al. 1996), and reward devaluation by feeding to satiety (Rolls et al. 1989; Critchley and Rolls 1996).

Despite many studies characterizing amygdala reward processing in animals, only one single-unit study addressed it in humans (Jenison et al. 2011). In this study neuronal correlates of explicit reward value in the amygdala were found in 3 patients with 2 sessions per patient and 50 trials per session during which 50 different food stimuli were presented once and rated for reward value. A total of 51 units were recorded, 16 of which were related to reward value. Our study provides an important confirmation of this result on a much larger dataset and extends the presence of a reward signal to other MTL regions and to orbitofrontal cortex. Most importantly, it is the first account of a task-invariant representation of subjective value in human amygdala neurons.

The amygdala not only enhances the perception of emotionally significant words under limited attention (Anderson and Phelps 2001) but modulates both encoding (Cahill et al. 1996) and consolidation of memories (Adolphs et al. 1997; LaBar and Phelps 1998; Canli et al. 2000; Cahill 2003). During this modulation it interacts with entorhinal cortex (Paz et al. 2006) and hippocampus (Phelps 2004). The former is important for linking visual cues to reward in the macaque (Liu and Richmond 2000; Sugase-Miyamoto and Richmond 2007) and hippocampal neurons encode reward in monkeys (Rolls and Xiang 2005). In rats, place cells can encode reward (Hölscher et al. 2003) similar to some of the units representing both value and image identity in this study (Fig. 6C). In light of these considerations, our data

support a role of entorhinal cortex and hippocampus in reward processing in humans. Since the reward system is involved in numerous diseases ranging from addiction (Li et al. 2014) via obsessive compulsive disorder to post-traumatic stress disorder (Glimcher 2009) its diverse functions in the modulation of perception, memory, and attentional resources, and automatic value representation described in this study should be topic of further investigations.

Supplementary Material

Supplementary data is available at *Cerebral Cortex* online.

Authors' Contributions

F.M. and I.F. designed the study. I.F. performed neurosurgical procedures. F.M. and I.F. collected the data. M.B. and F.M. analyzed the data. M.B. and F.M. wrote the article. S.K. assessed electrode localization. All authors discussed the results and commented on the article.

Funding

Grants from the Volkswagen Foundation (Lichtenberg Program), the German Research Council (DFG MO930/4-1 and SFB 1089), the US National Institute of Neurological Disorders and Stroke (NINDS grant R01NS033221), and the Dana Foundation.

Notes

We thank all of our subjects for their participation, E. Behnke, T. Fields and V. Isiaka for technical assistance with the recordings, A. Rangel for help with the design of the study, and C. Koch for fruitful discussion. *Conflict of Interest:* Authors declare no conflict of interest.

References

- Adolphs R, Cahill L, Schul R, Babinsky R. 1997. Impaired declarative memory for emotional material following bilateral amygdala damage in humans. *Learn Mem.* 4:291–300.
- Anderson AK, Phelps EA. 2001. Lesions of the human amygdala impair enhanced perception of emotionally salient events. *Nature.* 411:305–309.
- Baxter MG, Parker A, Lindner CC, Izquierdo AD, Murray EA. 2000. Control of response selection by reinforcer value requires interaction of amygdala and orbital prefrontal cortex. *J Soc Neurosci.* 20:4311–4319.
- Bechara A, Damasio H, Damasio AR, Lee GP. 1999. Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. *J Soc Neurosci.* 19:5473–5481.
- Belova MA, Paton JJ, Morrison SE, Salzman CD. 2007. Expectation modulates neural responses to pleasant and aversive stimuli in primate amygdala. *Neuron.* 55:970–984.
- Bermudez MA, Göbel C, Schultz W. 2012. Sensitivity to temporal reward structure in amygdala neurons. *Curr Biol.* 22:1839–1844.
- Bermudez MA, Schultz W. 2010. Reward magnitude coding in primate amygdala neurons. *J Neurophysiol.* 104:3424–3432.
- Brand M, Grabenhorst F, Starcke K, Vandekerckhove MMP, Markowitsch HJ. 2007. Role of the amygdala in decisions under ambiguity and decisions under risk: evidence from patients with Urbach-Wiethe disease. *Neuropsychologia.* 45:1305–1317.
- Cahill L. 2003. Enhanced human memory consolidation with post-learning stress: interaction with the degree of arousal at encoding. *Learn Mem.* 10:270–274.
- Cahill L, Haier RJ, Fallon J, Alkire MT, Tang C, Keator D, Wu J, Mcgaugh JL. 1996. Amygdala activity at encoding correlated with long-term, free recall of emotional information. *Proc Natl Acad Sci.* 93:8016–8021.
- Canli T, Zhao Z, Brewer J, Gabrieli JD, Cahill L. 2000. Event-related activation in the human amygdala associates with later memory for individual emotional experience. *J Soc Neurosci.* 20:RC99.
- Clark AM, Bouret S, Young AM, Murray EA, Richmond BJ. 2013. Interaction between orbital prefrontal and rhinal cortex is required for normal estimates of expected value. *J Neurosci.* 33:1833–1845.
- Critchley HD, Rolls ET. 1996. Hunger and satiety modify the responses of olfactory and visual neurons in the primate orbitofrontal cortex. *J Neurophysiol.* 75:1673–1686.
- Fried I, MacDonald KA, Wilson CL. 1997. Single neuron activity in human hippocampus and amygdala during recognition of faces and objects. *Neuron.* 18:753–765.
- Glimcher PW, editor. 2009. *Neuroeconomics: decision making and the brain.* 1st ed.. Amsterdam: Acad. Press.
- Hölscher C, Jacob W, Mallot HA. 2003. Reward modulates neuronal activity in the hippocampus of the rat. *Behav Brain Res.* 142:181–191.
- Jenison RL, Rangel A, Oya H, Kawasaki H, Howard MA. 2011. Value encoding in single neurons in the human amygdala during decision making. *J Soc Neurosci.* 31:331–338.
- Johnsrude IS, Owen AM, White NM, Zhao WV, Bohbot V. 2000. Impaired preference conditioning after anterior temporal lobe resection in humans. *J Soc Neurosci.* 20:2649–2656.
- Kendall MG, Smith BB. 1939. The problem of \$m\$ rankings. *Ann Math Stat.* 10:275–287.
- LaBar KS, Phelps EA. 1998. Arousal-mediated memory consolidation: role of the medial temporal lobe in humans. *Psychol Sci.* 9:490–493.
- Lak A, Stauffer WR, Schultz W. 2014. Dopamine prediction error responses integrate subjective value from different reward dimensions. *Proc Natl Acad Sci.* 111:2343–2348.
- Lee H, Ghim J-W, Kim H, Lee D, Jung M. 2012. Hippocampal neural correlates for values of experienced events. *J Soc Neurosci.* 32:15053–15065.
- Li X, Zeric T, Kambhampati S, Bossert JM, Shaham Y. 2014. The central amygdala nucleus is critical for incubation of methamphetamine craving. *Neuropsychopharmacology.* 40:1297–1306.
- Liu Z, Richmond BJ. 2000. Response differences in monkey TE and perirhinal cortex: stimulus association related to reward schedules. *J Neurophysiol.* 83:1677–1692.
- McDonald AJ. 1998. Cortical pathways to the mammalian amygdala. *Prog Neurobiol.* 55:257–332.
- Mormann F, Dubois J, Kornblith S, Milosavljevic M, Cerf M, Ison M, Tsuchiya N, Kraskov A, Quiroga RQ, Adolphs R, et al. 2011. A category-specific response to animals in the right human amygdala. *Nat Neurosci.* 14:1247–1249.
- Mormann F, Kornblith S, Quiroga RQ, Kraskov A, Cerf M, Fried I, Koch C. 2008. Latency and selectivity of single neurons indicate hierarchical processing in the human medial temporal lobe. *J Neurosci.* 28:8865–8872.
- Paton JJ, Belova MA, Morrison SE, Salzman CD. 2006. The primate amygdala represents the positive and negative value of visual stimuli during learning. *Nature.* 439:865–870.
- Paz R, Pelletier JG, Bauer EP, Paré D. 2006. Emotional enhancement of memory via amygdala-driven facilitation of rhinal interactions. *Nat Neurosci.* 9:1321–1329.

- Phelps EA. 2004. Human emotion and memory: interactions of the amygdala and hippocampal complex. *Curr Opin Neurobiol.* 14:198–202.
- Quiroga RQ, Nadasdy Z, Ben-Shaul Y. 2004. Unsupervised spike detection and sorting with wavelets and superparamagnetic clustering. *Neural Comput.* 16:1661–1687.
- Quiroga RQ, Reddy L, Kreiman G, Koch C, Fried I. 2005. Invariant visual representation by single neurons in the human brain. *Nature.* 435:1102–1107.
- Rolls ET. 2014. Emotion and decision-making explained: a précis. *Cortex.* 59:185–193.
- Rolls ET. 2016. Reward systems in the brain and nutrition. *Annu Rev Nutr.* 36:435–470.
- Rolls ET, Critchley HD, Mason R, Wakeman EA. 1996. Orbitofrontal cortex neurons: role in olfactory and visual association learning. *J Neurophysiol.* 75:1970–1981.
- Rolls ET, Sienkiewicz ZJ, Yaxley S. 1989. Hunger modulates the responses to gustatory stimuli of single neurons in the caudolateral orbitofrontal cortex of the macaque monkey. *Eur J Neurosci.* 1:53–60.
- Rolls ET, Xiang J-Z. 2005. Reward-spatial view representations and learning in the primate hippocampus. *J Soc Neurosci.* 25:6167–6174.
- Rushworth MF, Kolling N, Sallet J, Mars RB. 2012. Valuation and decision-making in frontal cortex: one or many serial or parallel systems? *Curr Opin Neurobiol.* 22:946–955.
- Sanghera MK, Rolls ET, Roper-Hall A. 1979. Visual responses of neurons in the dorsolateral amygdala of the alert monkey. *Exp Neurol.* 63:610–626.
- Stefanacci L, Amaral DG. 2002. Some observations on cortical inputs to the macaque monkey amygdala: an anterograde tracing study. *J Comp Neurol.* 451:301–323.
- Sugase-Miyamoto Y, Richmond BJ. 2007. Cue and reward signals carried by monkey entorhinal cortex neurons during reward schedules. *Exp Brain Res.* 181:267–276.
- Thorpe SJ, Rolls ET, Maddison S. 1983. The orbitofrontal cortex: neuronal activity in the behaving monkey. *Exp Brain Res.* 49:93–115.
- Walton ME, Behrens TEJ, Buckley MJ, Rudebeck PH, Rushworth MF. 2010. Separable learning systems in the macaque brain and the role of orbitofrontal cortex in contingent learning. *Neuron.* 65:927–939.
- Watabe-Uchida M, Zhu L, Ogawa SK, Vamanrao A, Uchida N. 2012. Whole-brain mapping of direct inputs to midbrain dopamine neurons. *Neuron.* 74:858–873.
- Wilson FAW, Rolls ET. 1993. The effects of stimulus novelty and familiarity on neuronal activity in the amygdala of monkeys performing recognition memory tasks. *Exp Brain Res.* 93:367–382.
- Wilson FAW, Rolls ET. 2005. The primate amygdala and reinforcement: a dissociation between rule-based and associatively-mediated memory revealed in neuronal activity. *Neuroscience.* 133:1061–1072.