To Bet, or Not to Bet: That Is the Question of SEF Spikes

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The ability of animals to monitor their own cognitive processes is called metacognition. In this issue of *Neuron*, Middlebrooks and Sommer (2012) show that single-unit activity of SEF neurons exhibit a metacognitive signal while monkeys perform a postdecision wagering task.

When you look into a convex mirror, you will see yourself looking into the mirror (Figure 1A). You might pick up the mirror and move it around your face. Then you will see yourself reflected at various angles under the control of your hand's movement. Like the mirror reflecting us, we are endowed with the ability to monitor our own thoughts and cognition from various aspects. This ability is termed metacognition (Flavell, 1979). For instance, if you are cramming for an upcoming history exam, you may decide to focus on the material that you feel you understand the least. Or when you are reading a difficult book, you may reread a paragraph if you feel you did not initially grasp its meaning, and in some cases you may look up background information in an encyclopedia. Metacognition is the process by which you make a judgment on the basis of introspection of your own cognitive state. In this way, metacognition allows you to assess and regulate the current state of your cognitive activity so that you can determine how to act in a given situation (Dunlosky and Metcalfe, 2009).

Localization of metacognitive functioning in the human brain was attempted in a neuropsychological study of specific frontal lesions (Schnyer et al., 2004) and in an fMRI study of healthy subjects (Kikyo et al., 2002; Maril et al., 2003). Some frontal areas were found to be recruited when participants experienced a "feeling of knowing" what was to be recalled (Kikyo et al., 2002). Metacognitive ability had been thought to be unique to humans; however, recent studies show that rhesus monkeys also exhibit metacognitive behavior when performing cognitive tasks (Hampton, 2001; Kiani and Shadlen, 2009; Kornell et al., 2007). Monkeys are capable of making reasonable "bets" on whether they were correct or incorrect in a perceptual or mnemonic test they had just taken. In this issue of *Neuron*, Middlebrooks and Sommer (2012) recorded the spiking activity of single neurons in the macaque frontal cortex during a metacognitive task (Figure 1B). This study is novel in its use of electrophysiology with high temporal and spatial resolution to capture a metacognitive process in macaque frontal cortex, a neural substrate that is shared by humans and monkeys.

The authors investigated the neuronal correlates of metacognition in this study using a postdecision wagering task (Middlebrooks and Sommer, 2011). This task comprised two stages (Figure 1B). In the first stage, monkeys performed an oculomotor delayed response to a presented cue stimulus (decision stage). Task difficulty was manipulated by randomly changing the time interval between the cue stimulus and the subsequent mask (stimulus onset asynchrony, SOA). After the decision (i.e., occulomotor response), and following a subsequent delay period, the monkeys chose one of two options by making another saccade (bet stage). One of the options ("high-bet") offered a larger reward only if the monkey made a correct saccade at the preceding decision stage, whereas the other option ("low-bet") guaranteed a smaller, but certain, reward regardless of whether the monkey made a correct decision. To earn the largest reward, the animals had to monitor their own decision in each trial and choose an appropriate option on the basis of a confidence in the decision, and this process is metacognitive. The authors conducted single-unit recordings while the animals performed this task, which enabled them to examine the metacognitive signal at the single neuron level. They recorded the neuronal activity from three different areas in the frontal cortex (frontal eye field [FEF], dorsolateral prefrontal cortex [PFC], and supplementary eye field [SEF]) and examined which of these areas is most involved in metacognition.

Behavioral analysis first revealed that the monkeys performed this task as expected: the animals indeed made a correct decision more frequently when they chose the high-bet compared to when they chose the low-bet. This was true for each SOA, indicating that the monkeys placed their bets on the basis of trial-by-trial monitoring of their own decision, and not just on the basis of task difficulty.

Single-unit activity during this task was then analyzed for the FEF, PFC, and SEF in the frontal cortex. First, the authors compared neuronal activity for correct and incorrect decisions at the decision stage and found that all three areas exhibited significant increases in activity when the decision was correct. They next focused on activity during the time period between the decision and bet stages (interstage period). The authors hypothesized that the neuronal activity during this period would probably link the animal's decision and the subsequent bet, and thus encode the metacognitive signal. If neuronal activity encodes the animal's metacognition, there should be differences in activity between high- and low-bet conditions even for the same preceding decision. During the interstage

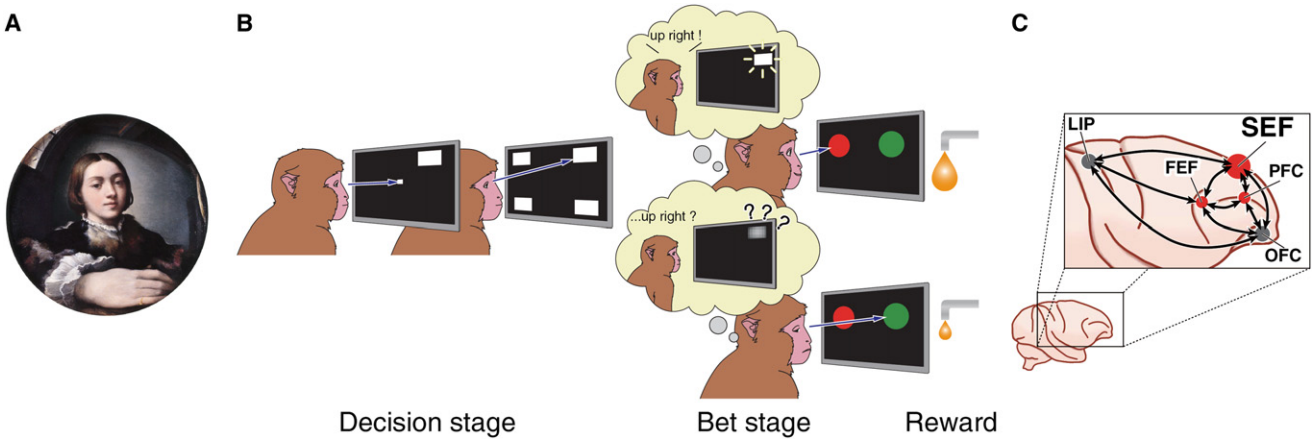

Figure 1. Metacognition in Macaque Monkeys: Frontoparietal Network for Decision Monitoring
(A) Metacognition is the ability to think about one's own thinking. In this picture, a man views himself reflected by a convex mirror (from Parmigianino's "Self-portrait in a Convex Mirror").
(B) In Middlebrooks and Sommer (2012), monkeys first detected and reported the location of a peripheral target (decision stage) and then made a bet based on their decision (bet stage). When the monkeys chose the "high bet" (red circle), they earned the maximum reward for a correct decision but faced a penalty of a timeout without a reward for an incorrect decision. When the monkeys chose the "low bet" (green circle), they earned a minimal reward irrespective of the correctness of the decision.
(C) Metacognition-related areas in which single-unit activity has been investigated so far. The red circles indicate the areas in which activity was recorded in the present study. The gray circles correspond to the areas targeted in monkeys by Kiani and Shadlen (2009) or in rats by Kepecs et al. (2008). The black arrows indicate anatomical connections (Cavada et al., 2000; Lynch and Tian, 2006).

period, the neuronal activity in FEF and PFC was indistinguishable when different bets were made following the same correct decision. However, SEF neurons exhibited significant differences in activity when high- and low-bets were made following the same correct decision. The activity was on average stronger for the high-bet compared to the low-bet. These results suggest that the activity of SEF neurons, but not that of PFC or FEF neurons, reflected the monkey's decision monitoring for the subsequent wagering.

The activity of SEF neurons has been shown to encode the animal's anticipation of a reward (Roesch and Olson, 2003; So and Stuphorn, 2010). Therefore, an important issue regarding the observed metacognitive signal is the involvement of reward anticipation. To address this, the authors examined differences in activity when the same bet was preceded by different (correct or incorrect) decisions. They hypothesized that SEF activity would be indistinguishable in these conditions if it encodes reward anticipation. They found that the activity of SEF neurons during the interstage period showed a significant difference between the conditions of correct and incorrect decisions followed by the same bet, suggesting that reward anticipation in and of itself does not explain the activity of SEF neurons. This is a good control in their paradigm; however, the relationships between reward anticipation and the two-alternative forced choice of bets might be more complicated than the authors assumed. The relationships between metacognitive signal and reward anticipation should be examined more closely from various points of view in future studies.

Metacognition-related neuronal activity has been shown at the single-neuron level in a few previous studies. In particular, Kiani and Shadlen (2009) examined the neuronal signal encoding choice certainty in monkeys using an opt-out task paradigm. First, the monkeys were presented with moving dot stimuli with a given level of coherence. Monkeys were then given two forced choices, one of which indicated the correct direction of the dot motion and offered a reward. In half of the trials, a third opt-out choice was also presented in which the monkeys could receive a smaller, but certain, reward without choosing a direction. The authors recorded single-unit activity in the lateral intraparietal area (LIP) during this task and found that when the animal chose the opt-out option, the activity of LIP neurons was intermediate (i.e., between the levels recorded when the correct target was located in and outside of the response field). The intermediate level indicates that the activity did not encode the saccadic target, suggesting that the activity of LIP neurons reflected monkey's certainty regarding the perceived direction. In this paradigm, the animal's decision and its monitoring could not be temporally segregated. In the present study, the decision stage and bet stage were temporally segregated with the linkage by the interstage period, so that the authors could extract the neuronal correlates of decision monitoring as a metacognitive process. The authors indeed found that the majority of SEF neurons that encoded decision monitoring during the interstage period also coded for the decision itself at the decision stage (i.e., different activity between correct and incorrect decisions) and discussed that the observed metacognitive signal of SEF neurons might have evolved from the decision signal. Both studies in monkeys, however, opened an important possibility that neuronal mechanisms underlying metacognitive functions can be tapped in the primate frontal and parietal cortices at the single-neuron level by devising an adequate behavioral paradigm. Furthermore, in a pioneering work

by Kepecs et al. (2008), they demonstrated that the activity of neurons in the rat orbitofrontal cortex (OFC) matched the model of the rat's uncertainty regarding their own past decision. Metacognitive signals in the corresponding area in monkeys should thus be examined in future studies, which will facilitate our understanding of the relationships between the metacognitive signals in different brain areas (Figure 1C).

The strength of the metacognitive signal observed in Middlebrooks and Sommer (2012) was several spikes per second on average, which is not a large proportion of all the spikes fired by these neurons. Therefore, readout mechanisms and the behavioral impact of the observed metacognitive signals should be considered carefully. This is related to the issue of across-areal neuronal circuitry for metacognition, which would include the SEF, LIP, and presumably OFC, among which anatomical connections have been identified (Figure 1C) (Cavada et al., 2000; Lynch and Tian, 2006). Clarifying the hierarchical relationships between these areas and differentiating their roles in metacognition should be the next step in understanding the neuronal circuitry that implements this cognitive process, which we humans profoundly exploit to lead our daily lives.

REFERENCES

Cavada, C., Compañy, T., Tejedor, J., Cruz-Rizzolo, R.J., and Reinoso-Suárez, F. (2000). Cereb. Cortex *10*, 220–242.

Dunlosky, J., and Metcalfe, J. (2009). Metacognition (Thousand Oaks: Sage).

Flavell, J.H. (1979). Am. Psychol. *34*, 906–911.

Hampton, R.R. (2001). Proc. Natl. Acad. Sci. USA *98*, 5359–5362.

Kepecs, A., Uchida, N., Zariwala, H.A., and Mainen, Z.F. (2008). Nature *455*, 227–231.

Kiani, R., and Shadlen, M.N. (2009). Science *324*, 759–764.

Kikyo, H., Ohki, K., and Miyashita, Y. (2002). Neuron *36*, 177–186.

Kornell, N., Son, L.K., and Terrace, H.S. (2007). Psychol. Sci. *18*, 64–71.

Lynch, J.C., and Tian, J.R. (2006). Prog. Brain. Res. *151*, 461–501.

Maril, A., Simons, J.S., Mitchell, J.P., Schwartz, B.L., and Schacter, D.L. (2003). Neuroimage *18*, 827–836.

Middlebrooks, P.G., and Sommer, M.A. (2011). J. Exp. Psychol. Learn. Mem. Cogn. *37*, 325–337.

Middlebrooks, P.G., and Sommer, M.A. (2012). Neuron *75*, this issue, 517–530.

Roesch, M.R., and Olson, C.R. (2003). J. Neurophysiol. *90*, 1766–1789.

Schnyer, D.M., Verfaellie, M., Alexander, M.P., LaFleche, G., Nicholls, L., and Kaszniak, A.W. (2004). Neuropsychologia *42*, 957–966.

So, N.Y., and Stuphorn, V. (2010). J. Neurophysiol. *104*, 2634–2653.

Losing the Lust for Life: A New Role for an Old Feeding Peptide?

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A recent paper in *Nature* (Lim et al., 2012) describes the effects of melanocortin receptors in the nucleus accumbens. The studies connect a hypothalamic peptide system with brain reward centers and show effects on specific neuronal populations and behavioral components of mood.

Food and Mood

It is hard to imagine something more integrated with our mood state than eating. The influences go in both directions, with intake affecting mood and mood states modulating eating. For example, depression can lead to either increases or decreases in intake. As with all complex neuropsychiatric conditions, elucidation of basic neurobiological mechanisms is a critical first step toward clarifying just how the brain integrates eating with emotions. A recent study from Robert Malenka and colleagues published in *Nature* identifies molecules, circuits, and neuronal pathways by which hypothalamic derived peptides can influence hedonic states (Lim et al., 2012). Specifically, the study establishes mechanisms by which stress can lead to reduced intake and anhedonia.

Melanocortins and Their Receptors—Taking a Hint from Metabolism

The melanocortin agonist, alpha-MSH, is derived from the precursor peptide POMC. The POMC neurons of the arcuate nucleus form the "stop" side of the hypothalamic feeding equation whereby activation of this population reduces intake. The paraventricular nucleus of the hypothalamus has been best studied as a site where the melanocortin MC4 receptor (MC4R) mediates these effects. However, the MC4R is broadly expressed in the brain, including the nucleus accumbens and dorsal striatum. Early work showed regulation of MC4R by opiates and a role for striatal MC4R signaling in cocaine reward (Alvaro et al., 2003; Hsu et al., 2005), and more recent studies have