used, this drug increases mGluR1 activity in the presence of glutamate by binding to a distinct site. Ro 677476 returned the AMPA/NMDA current ratio to normal levels in the shShank3 group, without affecting scrShank3 mice. PAM treatment also abolished the increase in rectification induced by shShank3 injection, suggesting the rescue of abnormal synaptic maturation.

Besides rescuing the molecular phenotype, Ro 677476 compensated for SHANK3 insufficiency at cellular and behavioral levels. Treatment partially restored the normal bursting activity of VTA DA neurons and increased social preference in shShank3 mice. Underscoring the developmental role of SHANK3, treatment with PAM at the appropriate developmental time led to changes lasting into adulthood.

In summary, Bariselli, Tzanoulinou *et al.*[3] provide convincing evidence that SHANK3 is important for synapse maturation in the VTA during early postnatal development[3]. Furthermore, the deficits in DA neurotransmission induced by a reduction of SHANK3 appear to mimic ASD. These findings provide a compelling molecular and circuit mechanism for the losses of social preference observed in the human Phelan-McDermid syndrome.

In addition to the direct impact of VTA SHANK3 loss on excitatory transmission and dopamine release, such a loss also is likely to exert a powerful influence on the development of excitatory synapses in ventral striatum, since dopamine regulates glutamate-dependent striatal synaptogenesis[11]. Coupled with the precocious corticostriatal hyperconnectivity recently reported in *Shank3* knockout mice[8], the total load of synaptic and circuit perturbations in the basal ganglia due to loss of this scaffold protein is clearly substantial. Yet the hope for more effective treatment of ASD is growing, as several positive and negative allosteric modulators of metabotropic glutamate receptors have shown therapeutic promise in ASD[9,12,13]. Bariselli, Tzanoulinou *et al.*[3] have now provided the field with a fundamental explanation for how this could occur, spurring on the development of improved therapies.

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The dynamic nature of value-based decisions

Katherine E Conen & Camillo Padoa-Schioppa

During a binary choice task, neuronal activity in monkey orbitofrontal cortex alternated between two network states. The internal dynamics revealed by a linear decoder correlated with the reaction time and with the eventual choice.

Numerous studies conducted in recent years indicate that key aspects of economic decisions take place in the orbitofrontal cortex (OFC)[1–3]. However, the precise mechanisms through which subjective values are compared during the decision process remain unclear. One difficulty in assessing these mechanisms comes from the uniqueness of every decision. Even when subjects are repeatedly offered the same two options, choices vary. Furthermore, even if the same choice is ultimately made, the time course of the decision process presumably varies from trial to trial, reflecting small changes in subjective values and/or other sources of neuronal variability[4]. These various elements pose a challenge to decision neuroscience. In a study published in this issue of *Nature Neuroscience*, Rich and Wallis[5] begin to address this challenge. By recording simultaneously from small populations of neurons, they were able to decode aspects of the decision dynamics within each trial. Their study shows that value representations in the OFC alternate between network states associated with the two options available in the trial, potentially reflecting internal deliberation.

In the experiments, rhesus monkeys chose between different rewards, which came in two types and in four sizes. Each reward was represented by a particular image, and sessions included choice trials (two rewards available) and non-choice trials (one reward available). The authors recorded from the OFC, collecting data from an average of ten neurons simultaneously. The main results are based on a linear discriminant analysis. Using data from non-choice trials, the authors trained a linear classifier to identify the size of the reward on the basis of population activity. Then the same classifier was run on data collected during choice trials, where the reward size was labeled as chosen, unchosen, or unavailable depending on what rewards were offered to the animal and on the eventual choice. The classifier was trained on one time bin (the time of peak decodability) in non-choice trials and tested separately at different time points in choice trials. Thus, for any given choice trial, any time bin, and each reward size, the authors calculated a posterior probability that represented the likelihood with which the classifier identified that reward size as the one presented to the animal. Finally, on the basis of these posterior probabilities, the authors defined an internal state of the network.

Within each trial, the neural network alternated mainly between the two states corresponding to the available options, the one ultimately chosen and the unchosen one (**Fig. 1**). Furthermore, when the analysis of single cells was conditioned on the state of the network, individual neurons were also found to alternate between the two reward sizes. The alternation between the two states of the network correlated with behavioral measures. Specifically, states associated with the chosen option were slightly more frequent and lasted longer than those associated with the unchosen option.

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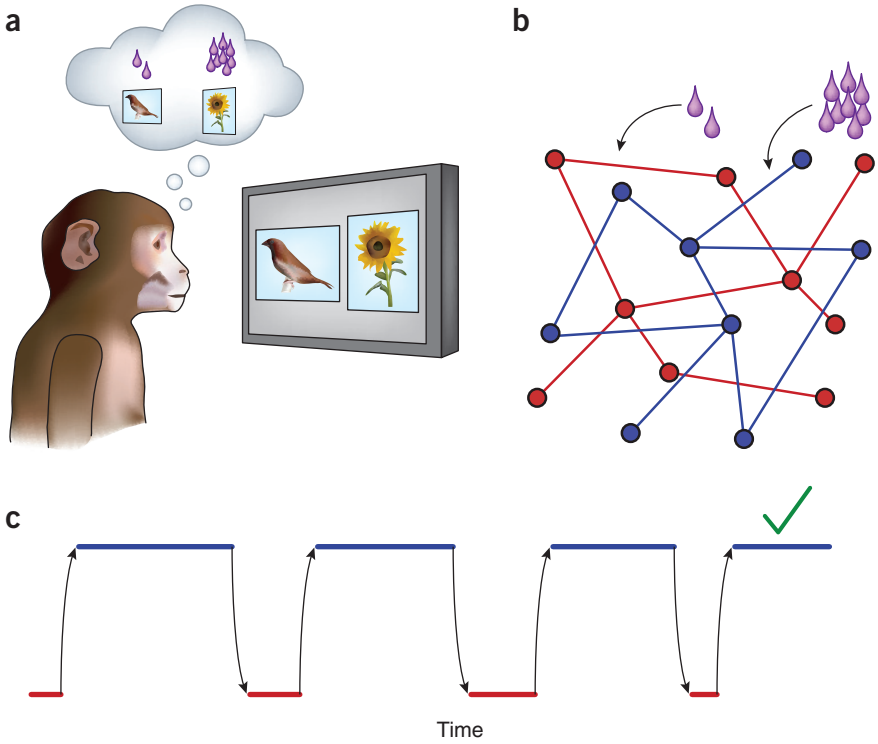

Figure 1 Conceptual summary of the results of Rich and Wallis[5]. (**a**) In the experiment, rhesus monkeys chose between rewards of different sizes, each associated with an arbitrary image. (**b**) A conceptual representation of the two network states, corresponding to the two options offered within each trial. Note that individual neurons participated in both states, although here, for clarity, the two states are depicted as separate networks. (**c**) Over the course of any one trial, the network alternated between the state associated with the option that was ultimately chosen (blue) and the state associated with the other, unchosen option (red). Periods spent in the chosen state were slightly more numerous and lasted slightly longer than periods spent in the unchosen state.

Furthermore, monkeys' responses were faster when the chosen option had high posterior probability relative to the unchosen option, particularly if this discrepancy occurred early in the trial. These results suggest that the network states captured by the linear classifier corresponded, at least to some degree, to the animals' mental states.

Some observations of this study are surprising when taken together with previous results. For example, on longer trials the authors found chance-level posterior probabilities for both the chosen and the unchosen options at the end of the decision time. This is unexpected because other work has found value- and decision-related signals in the OFC at this time[4,6]. A possible explanation for the discrepancy might be that the linear classifier was trained on non-choice trials, while the process of value comparison might only take place during choice trials. In this light, it is perhaps most appropriate to think of the states defined by Rich and Wallis[5] as capturing the assessment of the two options, as opposed to the competition between them. But even in the light of this distinction, population decoding is a potentially effective tool for examining value comparison because patterns of neuronal activity can be identified using unsupervised approaches[7,8].

The full potential of population decoding in the study of value-based decisions has yet to be determined. In this study, Rich and Wallis[5] were able to extract information about how the representation of the two options varied over time, possibly reflecting internal deliberation. This result is exciting, but it pertains only to one aspect of the decision process. Future work should assess whether measures based on this or similar approaches can also account for other aspects of decision making. Ideally, the analysis would provide an estimate of the time at which the decision is completed in each trial and trial-specific measures of relative value, motivation and decision confidence. Notably, population decoding is an established technique for studying movement planning and control[8–10]. Thus, researchers interested in using population decoding to study different aspects of choice might find some guidance in the work done in motor systems[7].

The study of Rich and Wallis[5] opens numerous avenues for future research. Here decoded value states were most prevalent shortly after offer presentation, suggesting that the neural signals captured by the classifier reflect some aspect of value assessment. At the same time, it is not clear whether and how these signals contribute to the decision. Perhaps most importantly, the neural circuit analyzed here with a linear decoder is almost certainly composed of functionally distinct neuronal populations, as has indeed been observed in other studies[4]. Describing the mechanisms through which value-based decisions are generated will ultimately require identifying the different components of this neural circuit and understanding their mutual interactions. As shown here, the analysis of small populations of neurons can provide dynamic information on single trials. A central challenge for future work will be to extend this approach and to capture the complexity of the neural circuit underlying value-based decisions. To do so, one promising avenue might be to combine population decoding with classification procedures based on the activity of individual cells.

In summary, while it is clear that OFC participates in economic decisions, there is no consensus on the mechanisms that underlie the comparison of different subjective values. Although Rich and Wallis[5] did not address this question directly, the linear decoding approach introduced in their study represents a significant step forward for the field. Their analysis highlighted changes in the state of the network over the course of a single trial, and these changes were meaningfully related to behavioral measures. A challenge for future research will be to investigate the decision dynamics within a single trial while accounting for the functionally distinct components of this neural circuit.

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