

for future research is how the value signal incorporates this aspect of a decision. Does it involve feedback from motor areas into the OFC, or does a different brain area encode this information? The latter seems more likely, as the OFC connects only weakly to motor areas⁵. Furthermore, the medial PFC in rats (which connects to both motor and reward areas) is critical for integrating effort and payoff information^{6,7}.

Further questions remain regarding choice behavior. Determining how much we value something is the first step, but despite our decision that a certain course of action is valuable, we often have trouble implementing

our choice. After all, how many New Year's resolutions make it to February? For most of us, this is a minor inconvenience, but for some, such as the morbidly obese, drug addicts, compulsive gamblers or individuals with eating disorders or obsessive-compulsive disorder, the inability to control choice behavior is more serious. Furthermore, there is evidence that these disorders involve OFC dysfunction^{8,9}, although its precise role in these illnesses remains unclear. By specifying the processes that underlie the control of choice behavior in healthy individuals, as Padoa-Schioppa and Assad have done, we can begin to understand what goes awry in these neuropsychiatric populations.

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Clearing obsolete NMDA receptors

The subunit composition of NMDA-type glutamate receptors at nascent synapses changes with synaptic maturation. Immature NMDA receptors that include NR3A subunits are distinguished by their low Ca^{2+} permeability and Mg^{2+} sensitivity. Mature NMDA receptors exclude NR3A subunits, are highly Ca^{2+} permeable upon stimulation, and are powerfully blocked by Mg^{2+} . Thus, the original juvenile receptor types need to be removed and exchanged for the mature types as development proceeds.

On page 611 of this issue, Pérez-Otaño and colleagues look into the mechanism by which NR3A-containing NMDA receptors are cleared from synapses in hippocampal cultures. Although it has been reported previously that the NR1 subunit (common to all NMDA receptors) coalesces at emerging synaptic sites in maturing cultures, the authors observed here that the NR3A subunit remained diffusely distributed along the dendritic membrane. Under baseline conditions, NR3A-containing receptors were internalized at much higher rates than receptors lacking NR3A. Inhibitors blocking either neural activity entirely, or NMDA receptor activity specifically, prevented the endocytosis of NR3A complexes.

How are NR3A-containing NMDA receptors targeted for preferential activity-dependent endocytosis? The authors found that the intracellular tail of NR3A, but not of other subunits, interacts with PACSIN1, a neuron-specific multivalent adaptor molecule that had already been implicated in regulation of endocytosis as well as the actin cytoskeleton. PACSIN1 linked NR3A to the clathrin-dependent endocytosis machinery, and expression of a fragment interfering with PACSIN1 inhibited NR3A internalization and increased NR3A localization at *bona fide* postsynaptic specializations. The figure is an artistic rendition of NR3A (green) 'escaping' the postsynaptic density, presumably aided by PACSIN1.

In vivo, the authors found that the onset of PACSIN1 expression correlates with the critical phase of postnatal synaptic maturation in juvenile rat forebrain. As PACSIN1 expression increases, NR3A expression decreases, consistent with the idea that PACSIN1 serves to clear NR3A-containing NMDA receptors from maturing active synapses. The data also suggest a hypothetical function for the NR3A subunit itself: its primary role may not be to confer specific channel characteristics to young NMDA receptors. Instead NR3A might target juvenile NMDA receptors for PACSIN1-mediated endocytosis at the appropriate time, allowing their replacement with mature NMDA receptors capable of sustaining Ca^{2+} -dependent synaptic plasticity such as long-term potentiation and long-term depression. NR3A knockout mice, which have been available for some years, show higher spine densities and greater NMDA currents as juveniles. Close inspection of these animals, as well as generation of PACSIN1-null mice, will reveal whether the intriguing mechanisms and hypotheses put forward by Pérez-Otaño and colleagues correctly describe *in vivo* maturation of glutamatergic synapses.

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