

The Neuroscientist Comments

Postsynaptic receptor trafficking and learning

One of the catechisms of contemporary neuroscience is that learning involves selective modifications in synaptic efficacy. Much of what we understand about synaptic mechanisms associated with learning has been derived from studies on long-term potentiation, and it has been suggested that the synaptic strengthening that occurs during LTP involves the addition of GluR1 subunit-containing AMPA-type glutamate receptors. Now Rumpel and associates (2005), using auditory fear conditioning, have tested the hypothesis that a learning-driven increase in GluR1 receptors at selective synapses underlies associative memory. Building on the putative role of the amygdala in acquisition and storage of fear memory traces, these investigators studied the role of GluR1-receptor trafficking at thalamo-amygdala synapses in associative fear conditioning. Using amplicon vectors to monitor and perturb AMPA receptor trafficking, these investigators first observed that there was little or no synaptic incorporation of GluR1 receptors within the lateral amygdala of naive rats. Next, they tested a key predication of the receptor trafficking hypothesis, that is, that conditioning should induce the incorporation of GluR1 receptors into thalamo-amygdala synapses, and they observed that associative fear conditioning is a powerful stimulus for incorporation of these receptors into synapses within the lateral amygdala that receives auditory input. Building on

these results, they next demonstrated that receptor trafficking induced by fear conditioning is not a generalized or global phenomenon but is rather restricted to a subset of synapses. Rumpel and associates next tested another predication of the trafficking hypothesis, that is, that synaptic delivery of endogenous GluR1 receptors is a prerequisite for acquisition of the condition response, and they observed that blockade of synaptic GluR1-receptor incorporation within the lateral amygdala disrupts the learning process underlying the lasting form of associative memory. Finally, these authors estimated the fraction of neurons with the lateral amygdala that must exhibit plasticity for fear conditioning to occur, and they found that memory was reduced if AMPA receptor synaptic incorporation was blocked in as few as 10% to 20% of neurons within the lateral amygdala. On the basis of these studies, the authors concluded that the encoding of memories within the lateral amygdala is mediated by AMPA receptor trafficking, is broadly distributed, and displays little redundancy. Future studies will undoubtedly focus on the question of whether these conclusions apply to other areas of the brain.

Rumpel S, LeDoux J, Zador A, Malinow R. 2005. Postsynaptic receptor trafficking underlying a form of associative learning. *Science* 308:83–8.

Vasopressin and oxytocin target different neurons in amygdala

The amygdala, of course, plays a key role in anxiety and fear behavior. The underlying circuitry involves efferents emerging from the central amygdala to the hypothalamus and brainstem, where they trigger the autonomic expression of fear. Consistent with the idea that selective gating of synaptic transmission through the central amygdala can modulate the fear response, recent observations link increased synaptic inhibition within the central amygdala with the anxiolytic effects of benzodiazepine medications and alcohol. Both vasopressin and oxytocin receptors are expressed within the central amygdala, but activation of vasopressin and oxytocin receptors oppositely affects fear and anxiety-related behaviors, with vasopressin enhancing aggressiveness, anxiety, and stress levels, and oxytocin decreasing anxiety and stress and facilitating social encounters and maternal behavior. Both vasopressin and oxytocin increase neuronal excitability within various brain regions including the central amygdala, raising the question of whether local neuronal networks are

involved in the opposite behavioral effects of these two transmitters. Now Huber and others (2005) have identified two distinct neuronal populations within the central amygdala, which act as parts of an inhibitory network, through which vasopressin and oxytocin modulate the integration of excitatory information from the basolateral amygdala and cortex, but in opposite manners. By modulating activity in central amygdala neurons in opposite ways through the activation of different neuronal populations within the central amygdala, vasopressin and oxytocin thus differently affect the integration of distinct afferents to the central amygdala, into a shared output to the autonomic nervous system. These new findings help to explicate the opposing roles of vasopressin and oxytocin in the fear response.

Huber D, Veinante P, Stoop R. 2005. Vasopressin and oxytocin excite distinct neuronal populations in the central amygdala. *Science* 308:245–8.

A neurobiology of economics?

As functional brain imaging has become more and more sophisticated, it has begun to be applied to increasingly complex paradigms including social behavior. The idea of finding brain correlates of “trust” has been, for some, a Holy Grail, but now a step appears to have been taken in that direction, in a study (King-Casas and others 2005) in which event-related fMRI was used to simultaneously monitor homologous regions of the brains of pairs of subjects as they played a multi-round trust game in which one subject assumed the role of an investor while the second assumed the role of a trustee in multiple (10) consecutive rounds of social interactions. In this game, the investor could invest any portion of \$20 with the other player (the trustee), and the money then appreciated to yield three times the investment, at which time the trustee decided how much of the tripled amount to repay to the investor. In each round, while both brains were studied, each player was confronted with the decision as to how much money to invest or return (i.e., how much to trust the other player). Forty-eight subject pairs were scanned in this study, which revealed that brain response magnitude tended to be

correlated with intention to trust on the next play of the game. Notably, reciprocal actions expressed by the investor tended to strongly predict changes in trust by the trustee and evoked two effects, one encoded by response magnitude and the other by response timing in the trustee brain, including changes in the head of the caudate nucleus, where response was greater for benevolent reciprocity (being generous in response to a defection by the trustee) than for malevolent reciprocity (repaying the trustee’s generosity with a breach of trust). The authors interpret their results as suggesting that the head of the caudate nucleus receives or computes information about the fairness of a social partner’s decision and the intention to repay that decision with trust. This complex set of experiments opens up as many questions as it answers but, if confirmed, may provide a step toward understanding the neurobiology of complex social interactions.

King-Casas B, Tomlin D, Anen C, Camerer CF, Quartz SR, Montague PR. 2005. Getting to know you: reputation and trust in a two-person economic exchange. *Science* 308:78–83.

Functional brain imaging: pushing the envelope

The development of functional brain imaging has clearly had a profound effect on neuroscience, and there is every reason to believe that over the coming decade, it will yield additional important insights about brain function and organization. Nevertheless, the usefulness of functional brain imaging has, thus far, been limited by its relatively low spatial resolution of a few millimeters. That may be changing, however, as illustrated by two recent articles that used sophisticated data analysis algorithms to obtain substantially higher (i.e., more fine-grained) spatial resolution. In the first of these studies, Kamitani and Tong (2005) used statistical algorithms and demonstrated that ensemble fMRI signals, collected from human subjects using a 3T magnet, in early visual areas such as V1, could predict with high reliability, within individual trials, visual stimulus orientations. The importance of this is that stimulus orientation is encoded within single cortical columns, which are smaller than a millimeter across. They also found that when subjects directed their attention to one of two overlapping orthogonal gratings, there was a bias of ensemble activity toward the attended orientation. This study shows that fMRI—using appropriate image analysis algorithms—can accurately differentiate subtle variations in perceived stimulus orientations on a trial-by-trial basis, with orientation-selective activity being most pronounced in visual areas V1 and V2 and progressively weaker in higher areas. In

the second study, Haynes and Rees (2005) report that it is possible to use fMRI with a 3T magnet to obtain direct measures of orientation-selective processing within V1. These investigators found subtle but reproducible biases to oriented stimuli within many parts of V1 and used multivariate pattern recognition to accumulate this information across the whole of V1. Remarkably, using this information, they were able to successfully predict which of two oriented stimuli a participant was viewing, even when that stimulus was rendered invisible by masking. Again, the evidence points toward orientation-selective processing of visual stimuli within human V1. These two studies on V1, taken together, represent an important step forward in unraveling the way in which the brain processes visual information. In addition, however, these studies show that it is possible, using currently available 3T scanners, to process data so that they can provide direct measurements of brain activity at the submillimeter level. These studies, and the analytical methods that they introduce, may portend similar advances in understanding other brain regions.

Haynes JD, Rees G. 2005. Predicting the orientation of invisible stimuli from activity in human primary visual cortex. *Nat Neurosci* 8:686–91.

Kamitani Y, Tong F. 2005. Decoding the visual and subjective contents of the human brain. *Nat Neurosci* 8:679–85.