So then, how could one turn on plasticity permanently without inducing homeostatic plasticity? Slutsky et al. devised an ingenious approach to solve this dilemma. Since biochemical processes are tuned to both the amplitude and frequency of Ca^{2+} signals, they specifically blocked weak synaptic events that would evoke low levels of Ca^{2+}, but not stronger correlated activity that would drive higher intracellular Ca^{2+} levels. They achieved this selective inhibition by taking advantage of the voltage-dependent properties of NMDA receptor $[Mg^{2+}]_o$ block. Increasing $[Mg^{2+}]_o$ levels from 0.8 to 1.2 mM did not change the excitability or resting state of neurons, but strongly reduced NMDA receptor-mediated currents and the associated Ca^{2+} changes near resting membrane potential (by $\sim$60%). However, at more depolarized potentials, in a range where the Mg^{2+} block was minimal, increases in $[Mg^{2+}]_o$ attenuated NMDA receptor activity to a lesser extent. Hence, the authors inferred that weak NMDA receptor-mediated EPSPs and their associated Ca^{2+} entry would be blocked, while the correlated activity that is strongly depolarizing and drives large Ca^{2+} influxes would remain relatively unaffected by increased $[Mg^{2+}]_o$. In contrast to the effects of global reduction of Ca^{2+} entry, which were lost after 2 days, this filtering of low-level NMDA receptor activity by modest increases in $[Mg^{2+}]_o$ led to a relatively long-lasting enhancement of low P_r synapse recruitabilty by theta burst stimulation. In addition, these effects of increasing $[Mg^{2+}]_o$ were reversible. The finding that a relatively small change within the physiological concentration range of this mineral can impact the degree of NMDA receptor activity and have a significant effect on the gating of plasticity is unprecedented. However, future experiments will need to exclude other potential targets of Mg^{2+} action, including voltage-gated Ca^{2+} channels (Yasuda et al., 2003), and indeed show that uncorrelated activity is blocked by this treatment.

The mechanisms underlying the unlocking of synapses by elevated $[Mg^{2+}]_o$ maybe multifaceted. Although the authors do not make it clear whether it involves the sensitization of the BDNF pathway, they find a new twist to this phenomenon when they look at the expression of NR2B. This was made in an attempt to compare their cultures to the developing nervous system, where immature, highly plastic synapses express NR2B. They found that increased $[Mg^{2+}]_o$ led to a relative increase in the role of NR2B receptors in NMDA receptor-mediated EPSCs. This increase in NR2B EPSCs was shown to be in part responsible for the gating of low P_r synapses by subsequent theta burst. In some ways, these results differ from recent studies showing that NR2B receptor expression is necessary for long-term depression and not long-term potentiation (Liu et al., 2004; Massey et al., 2004). However, the results are consistent with previous findings showing that ectopic expression of NR2B can increase learning and memory as well as LTP (Tang et al., 1999).

Clearly, more work is necessary before we fully understand the implications of the current findings for plasticity in the mature nervous system. The intricate connections between correlated bursting activity, BDNF, and NMDA receptor function still need to be elucidated. Future directions will also involve selectively manipulating the levels of uncorrelated versus correlated NMDA receptor-mediated activity in vivo. Although more work needs to be done, Slutsky et al. have led us through some of the tortuous interactions of pathways initiated by dynamic Ca^{2+} signals and have provided us with the first glimpse of the process by which synaptic plasticity can be gated at quiescent synapses.

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Selected Reading

Kang, H., Welcher, A.A., Shelton, D., and Schuman, E.M. (1997). Neuron *19*, 653–664.

Liu, Z., Ren, J., and Murphy, T.H. (2003). J. Physiol. *553*, 473–488.

Liu, L., Wong, T.P., Pozza, M.F., Lingenhoehl, K., Wang, Y., Sheng, M., Auberson, Y.P., and Wang, Y.T. (2004). Science *304*, 1021–1024.

Massey, P.V., Johnson, B.E., Moult, P.R., Auberson, Y.P., Brown, M.W., Molnar, E., Collingridge, G.L., and Bashir, Z.I. (2004). J. Neurosci. *24*, 7821–7828.

Murphy, T.H., Worley, P.F., and Baraban, J.M. (1991). Neuron *7*, 625–635.

Murthy, V.N., Sejnowski, T.J., and Stevens, C.F. (1997). Neuron *18*, 599–612.

Murthy, V.N., Schikorski, T., Stevens, C.F., and Zhu, Y. (2001). Neuron *32*, 673–682.

Ryan, T.A., Ziv, N.E., and Smith, S.J. (1996). Neuron *17*, 125–134.

Slutsky, I., Sadeghpour, S., Li, B., and Liu, G. (2004). Neuron *44*, this issue, 835–849.

Tang, Y.P., Shimizu, E., Dube, G.R., Rampon, C., Kerchner, G.A., Zhuo, M., Liu, G., and Tsien, J.Z. (1999). Nature *401*, 63–69.

Turrigiano, G.G., and Nelson, S.B. (2004). Nat. Rev. Neurosci. *5*, 97–107.

Yasuda, R., Sabatini, B.L., and Svoboda, K. (2003). Nat. Neurosci. *6*, 948–955.

Neural Processing at the Speed of Smell

Olfaction is typically described as behaviorally slow, suggesting neural processes on the order of hundreds of milliseconds to seconds as candidate mechanisms in the creation of olfactory percepts. Whereas a recent study challenged this view in suggesting that a single sniff was sufficient for optimal olfactory discrimination, a study by Abraham et al. in this issue of *Neuron* sets out to negate the challenge by demonstrating increased processing time for discrimination of similar versus dissimilar stimuli. Here we reconcile both studies, which in our view together support the notion of a speed-accuracy tradeoff in olfactory discriminations

that are made within about 200 ms. These findings are discussed in light of the challenges related to defining olfactory perceptual similarity in nonhuman animals.

> Presently, we were aware of an odour gradually coming towards us, something musky, fiery, savoury, mysterious,—a hot drowsy smell, that lulls the senses, and yet enflames them,—the truffles were coming.

–William Makepeace Thackeray (1811–1863)

Thackeray aptly described an odor percept that gradually evolved over time. Indeed, whereas several lines of evidence suggest that the olfactory percept is spatially encoded within the olfactory bulb (Leon and Johnson, 2003), other lines of evidence point to the role of temporal coding in the formation of the olfactory percept (Laurent, 2002). Temporal patterns of neural activity throughout the olfactory system are influenced by odorants. This is true of activity at both the low and high gamma band (40–60 and 60–100 Hz), the beta band (15–30 Hz), and the theta band that corresponds to sniffing (4–8 Hz), as well as much lower frequency ranges reflected in changing neural firing patterns that evolve over hundreds of milliseconds to seconds (Laurent, 2002). While it is clear that odorants affect neural activity at these frequencies, it remains unclear exactly whether and how these temporal patterns shape the olfactory percept.

In general, discrimination between perceptually similar objects is more difficult than discrimination between perceptually dissimilar objects. Therefore, if discrimination time is held short and constant, one would expect poorer performance in discriminations of similar odorants (difficult) and better performance in discriminations of dissimilar odorants (easy). In turn, if performance accuracy is held constant, one would expect slower performance in discriminations of similar odorants (difficult) and faster performance in discriminations of dissimilar odorants (easy). These tradeoff scenarios are two sides of the same coin. Furthermore, if these expectations are not maintained, one could argue against a functional role for slow temporal neural processes in these tasks. In other words, if both easy and extremely difficult olfactory discriminations were made with equal accuracy within equally short durations, say 200 ms, one could argue that neural processing at 1000 ms poststimulus is irrelevant to the discrimination process.

It was in this context that recent psychophysical results obtained in rats by Uchida and Mainen have been framed (Uchida and Mainen, 2003). Specifically, Uchida and Mainen measured sampling time during two-alternative forced-choice olfactory discriminations between pairs of odorants or odorant mixtures that they considered dissimilar (easy discriminations) and pairs of odorants or odorant mixtures they considered similar (difficult discriminations). They concluded by stating that "speed of discrimination was independent of odor similarity," and hence there was no behavioral evidence for the significance of slow temporal coding in olfaction. That said, the data in Figure 5A of Uchida and Mainen in fact strongly suggest a tradeoff between accuracy and speed, but only up to the 200 ms point. Rats often employ sniff inhalations of only 52 ms in duration

(Youngentob et al., 1987, and Figure 6 in Mainen and Uchida), thus enabling two sniffs within this time period. The authors acknowledged this speed-accuracy tradeoff in their text, but did not focus on it in their conclusions.

In this issue of *Neuron*, Abraham et al. present a set of similar experiments in mice, albeit using a different paradigm (Abraham et al., 2004). Abraham et al. trained mice on a go/no-go discrimination task. At each trial, a mouse poked its nose into a sniff port to receive one of two odorants. One odorant signaled that a reward would be delivered within the sniff port, so the mouse kept its nose within the port. A second odorant signaled that no reward would be delivered, so the mouse naturally retracted its nose from the port. The time between odorant delivery and nose retraction in response to the unrewarded odorant was considered to be the time to discrimination. The authors tested pairs of simple monomolecular odorants, as well as pairs of binary odorant mixtures. For example, using odorants A and B, a pair of mixtures may consist of one mixture containing 0.4% A + 0.6% B + 99% mineral oil and a second mixture containing 0.4% B + 0.6% A + 99% mineral oil. One such mixture signaled imminent reward, whereas the other mixture signaled no reward, thus meriting nose retraction. The authors used binary mixtures because they expected them to be more similar than their constituents alone and thus more difficult to discriminate (e.g., discriminating a 1% A solution from a 1% B solution was predicted to be easier than discriminating a 0.4% A + 0.6% B solution from a 0.4% B + 0.6% A solution).

They found that equally accurate (∼90%) olfactory discriminations were significantly faster when they were between two odorants that they considered dissimilar (easy discriminations) as compared to two odorant mixtures that they considered similar (difficult discriminations). In order to confirm their predictions concerning odorant similarity, the authors then conducted optical imaging experiments of odorant-induced neural activity patterns on the surface of the olfactory bulb. They found that the binary mixtures produced patterns of activity that were much more similar to each other than were the patterns induced by the individual components, and they concluded that these mixtures were therefore "highly similar stimuli." In general, the authors concluded that their results revealed "a tradeoff between accuracy and speed," and described their own results as "in striking contrast" to those of Uchida and Mainen.

Both Uchida and Mainen and Abraham et al. provided a tour de force of methods and analysis that yielded beautiful results. Both used psychophysics to probe neural coding. It was psychophysics that initially paved the way to elucidating coding in vision and audition, and here these authors lead the way in olfaction. Furthermore, so often one encounters representations of data that have been fitted, normalized, smoothed, etc., to a point where the reader can get no real feel for the data. Both of these manuscripts consist of a heartening departure from this unfortunate trend. The reader knows exactly what was done and exactly what the data looked like. Indeed, it is this clarity that enabled us here to suggest an interpretation of the data that differs from that offered by both groups of authors.

We find that the results of Uchida and Mainen and

Abraham et al. were in fact not contradictory, only their interpretations were. The results were not contradictory due to the very different behavioral profile in both studies. In Uchida and Mainen, the task was designed such that rats benefited from speed and could receive a high frequency of reward even when performing poorly in the most difficult task. Thus, the different discriminations yielded differing levels of accuracy. Whereas "easy" discriminations were performed at ~90% accuracy, "difficult" discriminations were performed at ~60% accuracy. In Abraham et al., mice did not benefit from speed and were at over 90% accuracy across all conditions. While in one experiment time was constant as performance varied, in the second experiment performance was constant as time varied (compare Figure 5A in Uchida and Mainen to Figure 5A in Abraham et al.). In other words, these two experiments correspond to the two sides of the same coin previously described and together depict a coherent picture that supports a speed-accuracy tradeoff in olfaction. This tradeoff, however, does not prove a functional role for slow temporal processing in olfaction, it merely permits it. Both studies suggest a tradeoff up to ~200 ms. Future studies might employ different olfactory tasks, or modifications of the current discrimination tasks (by manipulating motivation and reward), in an effort to create a task that would engage the animal for longer periods of time before decision making. Such behavioral tasks would permit a more direct test of the neural process of interest, namely, firing patterns that evolve over hundreds of milliseconds to seconds.

Having determined that there is a tradeoff between accuracy and speed in olfactory tasks, we would like to pause and ask whether either group can in fact say with confidence what task their subjects were performing? Both manuscripts claim that their task was discriminating stimuli differing in their similarity. Although neither manuscript says this explicitly, it is implicit that their measures of similarity correspond to perceptual similarity. The method used by both manuscripts to measure similarity of odorants was to compare patterns of spatial activity on the surface of the olfactory bulb as revealed by optical imaging. Yet the nature of the link between these patterns and the olfactory percept is unknown, and the assumption that similarity in spatial distribution of activation on the surface of the olfactory bulb is tantamount to perceptual similarity, although tempting, is based on theory, not fact. This concern was partially mitigated by the use of mixtures. It is indeed intuitively reasonable that binary mixtures of very close proportions are perceptually more similar to mixtures of the same odorants in highly disparate proportions or to their constituents alone. However, there is a real possiblity that when using binary mixtures, rodents are simply focusing on the concentration of one component and making a monomolecular change in intensity judgment. In an effort to control for this, Abraham et al. tested mice on discriminations of two concentrations of the same odorant, choosing concentrations that reflected that odorant's proportion in the mixture previously tested (e.g., 0.4% A vers 0.6% A). They found that this task took mice much longer to perform than did the mixture task and that final accuracy was lower. They concluded from this that the binary mixture discrimina-

tions reflected processes involving both odorants. One can, however, suggest an alternative interpretation of this control study that also reflects processes involving both odorants. The right kind of background can enhance or interfere with judgments about the foreground. Taking a visual analog of the mixture problem, suppose that in each trial one is presented with one of two white squares on a black background and asked to judge its intensity (as the higher or lower of a set of two possibilities). To do the task, one is essentially comparing the intensity of the white square with the intensity of the background. If the two white squares are both relatively bright compared to the background, this would be a difficult task. This is analogous to the olfactory task of trying to distinguish, say, a 0.4% A from a 0.6% A concentration (the control study). Now, instead imagine the task where on each trial one of two white squares is presented with the other white alternative as background. The task of determining whether the central square is the lighter or darker alternative is now relatively easy. This is analogous to the situation where a binary mixture is either a 0.4% A + 0.6% B solution or a 0.4% B + 0.6% A solution. In both cases, the task is an intensity judgment for odorant A, but the presence of a background changes the ease of the task. Recent findings concerning receptor events in olfaction further support this alternative interpretation, in that individual odorants within a mixture act as antagonists at the level of individual receptors, thereby suppressing some of the signaling pathways activated by structurally related compounds (Firestein, 2004).

All in all, Abraham et al. do a masterful job of addressing the inherent uncertainty as to the elements of the task an animal attends to in an olfactory psychophysics task. This uncertainty, however, may best be addressed by replicating these experiments in humans. Various psychophysical results obtained in humans support the notion of a tradeoff between task complexity and speed in olfaction. Whereas preattentive odorant-dependent modifications of sniffing occur in humans within 160 ms of sniff onset (Johnson et al., 2003) and simple olfactory discriminations can be made within ~400 ms (Laing, 1986), more complex discriminations can take 2 s and more (Wise and Cain, 2000), and restricting sniff duration hampers performance accuracy (Sobel et al., 2000). Most importantly, human subjects can be explicitly instructed to perform similarity judgments, a tried and true method in psychophysics. Although laboratory animals have been used in psychophysical similarity judgments in vision and audition, this was generally done after the rules that link the physical stimulus and resultant percept were well characterized. It is no coincidence that these rules were first derived using human psychophysics. Both the trichromatic and opponent-process theories of vision and the functional significance of binaural processing in audition were all first elucidated in humans, where a verbal report of the percept could be obtained. Only after these rules were defined were they tested in animals and their physiological counterparts identified. Thus, our objection is not criticism of the work of Uchida and Mainen or Abraham et al., but rather criticism of our own work and field (human olfactory psychophysics), which has failed at present to generate

a human behavior-based theory of the link between the olfactory stimulus and olfactory percept.

Finally, we would like to conclude by highlighting a point of agreement across these studies. Both studies agree that specific percepts and discriminations can be generated rapidly, within the 200 ms range. These time frames combine with similar time frames revealed in human odorant-dependent sniff modulation (Johnson et al., 2003) to suggest that olfaction can be fast and should not be thought of as strictly a slow process. Vision is commonly thought of as a fast process. However, whereas visual detection can be very fast, visual discrimination can be slow, on the order of seconds, depending on the task (Luce, 1986). Similarly, whereas some olfactory computations and perceptual discriminations are undoubtedly reliably made within less than 200 ms, others evolve over time. Thus, Thackeray may have known within less than 200 ms that an odorant was present, but we think that it may have been nearly seconds-worth of processing, starting with rapid spatiotemporal mechanisms (Spors and Grinvald, 2002), followed by a slower evolution of firing patterns, all influenced by top-down modulatory input (Kay and Freeman, 1998) related to past memories (Wilson and Stevenson, 2003), before he could safely conclude—the truffles were coming!

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Selected Reading

Abraham, N.M., Spors, H., Carleton, A., Margrie, T.W., Kuner, T., and Schaefer, A.T. (2004). Neuron *44*, this issue, 865–876.

Firestein, S. (2004). A code in the nose. Science's STKE, pe15. DOI: 10.1126/stke.2272004pe15.

Johnson, B.N., Mainland, J.D., and Sobel, N. (2003). J. Neurophysiol. *90*, 1084–1094

Kay, L.M., and Freeman, W.J. (1998). Behav. Neurosci. *112*, 541–553.

Laing, D.G. (1986). Physiol. Behav. *37*, 163–170.

Laurent, G. (2002). Nat. Rev. Neurosci. *11*, 884–895.

Leon, M., and Johnson, B.A. (2003). Brain Res. Brain Res. Rev. *42*, 23–32.

Luce, R.D. (1986). Response Times (Oxford: Oxford University Press).

Sobel, N., Khan, R.M., Hartley, C.A., Sullivan, E.V., and Gabrieli, J.D. (2000). Chem. Senses *25*, 1–8.

Spors, H., and Grinvald, A. (2002). Neuron *34*, 301–315.

Uchida, N., and Mainen, Z.F. (2003). Nat. Neurosci. *6*, 1224–1229.

Wilson, D.A., and Stevenson, R.J. (2003). Neurosci. Biobehav. Rev. *27*, 307–328.

Wise, P.M., and Cain, W.S. (2000). Chem. Senses *25*, 247–265.

Youngentob, S.L., Mozell, M.M., Sheehe, P.R., and Hornung, D.E. (1987). Physiol. Behav. *41*, 59–69.

No About Face on Houses in the Fusiform Face Area!

Yovel and Kanwisher (this issue of *Neuron*) altered upright and inverted face and house characteristics during a same-different task. The right fusiform face area (FFA) was more active to faces than houses but, unlike behavior, was unaffected by spatial configuration or parts manipulations. These data raise interesting questions regarding the relationship of brain activation to observed behavior.

The excellent fMRI study described in this issue of *Neuron* (Yovel and Kanwisher, 2004) is built on a very rich bedrock of human behavioral literature on face recognition. Behavioral impairments in face recognition in normal subjects can be induced by inverting or altering the spatial relationships between the parts in the face—as shown in classic papers such as Yin (1969) and Sergent (1984) and an early review by Valentine (1988). The current study adds to the debate regarding the putative role of the FFA in face processing. The FFA and its specificity to face processing was originally proposed by Kanwisher et al. (1997) and McCarthy et al. (1997), questioned by Gauthier (e.g., Gauthier et al. 2000), and most recently the debate has been continued by Grill-Spector et al. (2004) and Rhodes et al. (2004).

Yovel and Kanwisher's fMRI study is important for a number of reasons. First, they have made a set of fairly elaborate predictions (see their Figure 2) for behavior and observed activation patterns in the FFA based on the extensive behavioral literature and on previous neuroimaging studies. Second, they test these hypotheses on regions of interest in the right and left FFA defined a priori using a functional localizer task. The stimulus categories selected in the activation task have been well tested in the behavioral literature and, importantly, activation conditions do not appear to be confounded by difficulty. Third, activation outside the right and left FFA, in regions sensitive to objects relative to faces, has been examined. Fourth, the knowledge gained in this study has provided new insights into how the FFA and surrounding ventral extrastriate regions respond to these experimental manipulations and raises a number of questions for future research.

Yovel and Kanwisher's data indicate that the right FFA responds vigorously to the presence of a face and is not influenced by parts or configural judgments. The right FFA seems to act as a face detector—consistent with the concept of the domain-specific mechanism. Contrast these data to the behavior of the left FFA: while there was no difference in activation strength for parts versus configuration judgments for faces, significantly greater left FFA activation was observed for judgments of changes in house parts relative to configuration. Like the right FFA, the left FFA also responded much more vigorously to faces than houses. Unlike its right counterpart, however, the left FFA had greater activation for parts relative to configural judgments for houses. This suggests that activation in the left FFA is influenced by the type of judgment being made on nonface stimuli.