

terneurons and ventral motor neurons. Both cell types appear to derive from unitary progenitor domains expressing unique transcription factor profiles that may be established shortly after neural tube closure by extrinsic cues derived from dorsal and ventral sources. Both cell types undergo a protracted secondary maturation that serves to elaborate subtype identities, which may be influenced largely by local intercellular interactions rather than earlier extrinsic cues, whose effects may be greatly diminished in the rapidly enlarging spinal cord. However, the mechanisms that function during these later times will likely differ in dorsal interneurons and motoneurons. Motoneurons are organized into pools of functionally equivalent cells and may utilize retinoid signaling and differential ETS gene expression to generate differences among subtypes (Jessell, 2000). In contrast, the current studies show that dorsal horn interneurons develop as intermingled populations of molecularly distinct cells, which instead suggests that local lateral inhibition mechanisms, such as those mediated by Notch signaling, may play a more prominent role.

In summary, the papers from Birchmeier's and Goulding's labs demonstrate that Lbx1 promotes the differentiation of multiple dorsal interneuron lineages. In this regard, its closest equivalent in ventral cells may be Lhx3, which appears to function postmitotically in both motor neuron and ventral (V2) interneuron differentiation (Sharma and Peng, 2001). Thus, while similar mechanisms appear to be employed by differentiating neurons in both the dorsal and ventral spinal cord, these studies provide a firm basis on which to further elaborate the mechanisms that distinguish dorsal and ventral horn cells from each other during embryogenesis.

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Multisensory Integration in Cortex: Shedding Light on Prickly Issues

Interactions between different sensory modalities can be observed in unimodal areas of the cortex, as revealed by recent neuroimaging studies. A new report by Macaluso and colleagues (Macaluso et al., 2002 [this issue of *Neuron*]) shows that crossmodal effects of tactile stimulation in visual cortex critically depend on the spatial congruence of multisensory inputs. This work is discussed in relation to neural and computational models of multisensory integration.

Many ordinary events in the physical world—a fly unsuccessfully trying to escape through a closed window, onions sizzling in a frying pan, a handshake—produce signals in several sensory modalities simultaneously. Although much information about such events can be extracted by treating these signals one modality at a time, a very important source of information lies in their spatial and temporal congruence. Our brain is exquisitely attuned to multisensory correlations which it uses to modulate and refine perceptual analysis. There are numerous examples of how perception can be enhanced, but also biased, by the integration of sensory signals across modalities: low-contrast or noisy visual and sound stimuli can be combined to improve spatial localization. Yet a salient visual stimulus readily “captures” the perceived origin of a sound source in the well-known ventriloquist effect. Speech is perceived more clearly when the speaker's lips are visible and it is distorted if the lip movements are rendered discrepant with the heard sound (McGurk and MacDonald, 1976). Being able to see one's arm improves the spatial resolution of tactile discrimination when two (unseen) pinpoint stimuli are applied near one another on the skin surface, and this effect can be further enhanced by simply magnifying the image of the arm (Kennett et al., 2001). A striking illusion can also be produced when you rub both hands together and the frequency of the accompanying rubbing sound is artificially increased: the perceived roughness of the stimulus can be enhanced to the point that subjects report the sensation of having a leaf of parchment paper between their rubbing hands (Jousmaki and Hari, 1998). Finally, even trained French enologists can be fooled by white wine tinted with a few drops of odorless red dye and describe its olfactory structure with characteristic red-wine terms (Morrot et al., 2001)!

Such phenomena underscore the importance of multisensory integration in assisting perceptual decisions. Classically, crossmodal effects have been attributed to neuronal interactions in multisensory convergence areas such as the superior colliculus (Stein and Meredith, 1993) or the parietal lobe (Hyvärinen, 1981). However, important recent work using functional neuroimaging is challenging this view with reports of multisensory interactions in unimodal areas such as the auditory (Calvert et al., 2000) and visual (Macaluso et al., 2000) cortices. The exact mechanisms through which, say, a tactile stimulus is able to exert a modulation on visually evoked activity in the occipital cortex is not fully understood

yet. Back projections from higher order multisensory integration areas of the cortex might mediate such effects, but it is worth noting that views of cortical connectivity are also evolving and that direct routes between unimodal areas which bypass the association cortex are being uncovered (Falchier et al., 2002).

One very important issue, above and beyond the question of the anatomical circuitry involved, concerns the nature of the neural computations required for multisensory integration to be accomplished. Indeed visual, auditory, and somatosensory stimuli are not represented in the same way in their respective cortical projection fields and thus cannot be compared directly. This is because sensory maps are organized according to the geometry of the corresponding receptor surfaces: the bite of a mosquito on my hand is represented in the somatosensory cortex in a skin-based frame of reference, while the image of the culprit in the visual cortex is coded in a retinal frame of reference. A minimal requirement for visuo-tactile integration is that the signals arising in the two modalities be assigned a common spatial origin, and this means that signals generated in one modality must be recoded into the reference frame of the other modality, or that both signal sources be recoded into a more abstract reference frame. Furthermore, since the retinal location of a tactile stimulus will shift whenever the hand is displaced or a change in gaze direction occurs, its spatial coordinates must be continuously updated. In the cortex, coordinate transformations of sensory information have been shown to take place in the parietal and premotor multimodal areas (see Duhamel et al., 1997; Graziano et al., 1997), and the computations that are involved have been analyzed with the aid of biologically constrained neuronal models (Denève et al., 2001).

In this issue of *Neuron*, Macaluso and collaborators show that these computations must indeed be taking place in order for a tactile stimulus to influence activity in human visual cortex. In a previous report (Macaluso et al., 2000), these authors had shown that neural activity in the visual cortex (as measured with fMRI) is stronger when a light source is flashed near the tip of the index finger while a vibration is applied to that finger, as compared to the light stimulus alone. This initial study provided evidence for crossmodal interaction in parts of the cortex which up to this point had been considered strictly visual, e.g., the lingual and fusiform gyri. However, the design of the experiment was such that the spatial relation between the stimulated retinal field and the stimulated finger was fixed. Therefore, a critical question remained unanswered: is crossmodal enhancement mediated by direct links between visual and somatosensory regions within the same cerebral hemisphere, or does it require a more complex spatial integration of the respective location of visual and tactile stimuli? In this new study, a refinement of the original paradigm allowed the authors to tease apart these two explanations. Through a simple manipulation of ocular fixation, the retinal and somatosensory stimuli could be addressed to opposite cerebral hemispheres without altering their alignment in external space. For instance, in one fixation condition, the visual stimulus presented above the index finger fell into the left visual field and thus activated the right visual cortex, while the simulta-

neous tactile stimulus activated the left somatosensory cortex. Conversely, the two stimuli could be addressed to the same hemisphere but in nonmatching spatial locations. This occurred when the right index finger was located to the left of the gaze axis and a light was turned on in the right visual field. The results were clearcut: as predicted from the previous study, crossmodal enhancement took place within visual cortex but, critically, only when the visual and tactile stimuli coincided in external space. Bimodal stimulation at noncongruent spatial locations resulted in reduced rather than enhanced visual responses.

This means that crossmodal interactions are spatially specific and not merely due to stimulation of two sensory modalities rather than one. Furthermore, these results imply that tactile and visual sensations interact through brain structures which can update information about the relative spatial alignment of the respective sensory maps, by taking into account postural information. Macaluso et al. varied eye position but kept the remaining components of body posture fixed. A prediction that would follow from their hypothesis is that such crossmodal “boosting” should also depend on the other postural variables that determine spatial congruence of multimodal stimuli, e.g., head, arm, and hand position.

Interestingly, a neural model designed to perform multisensory coordinate transformations using the known properties of cortical neurons actually predicts the crossmodal effects revealed in unimodal visual cortex by Macaluso and his collaborators (Denève et al., 2001). Indeed, because the primary purpose of the simulated network was to achieve a full mapping of information across sensory modalities, e.g., from tactile to visual or vice versa from visual to tactile, the sensory “input” modules were interconnected via an intermediate multisensory representation (similar to that found in the posterior parietal lobe of nonhuman primates) using forward and backward connections. Such a recurrent architecture results in a multidirectional flow of information across the network with no rigid distinction between input and output, allowing activity at one entry point of the network to affect activity at another entry point. Further experimental work along the line of that conducted by Macaluso and colleagues will be necessary to test the validity of such a theoretical account of multisensory integration. For instance, it is as yet unclear whether there exists a symmetrical influence of visual input onto activity evoked in the somatosensory cortex. Finally, one can hope that future imaging experiments will help reveal more directly the brain regions that perform the intermediate operations needed to blend the different sensory modalities within a spatially coherent framework.

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Correlations between the fMRI BOLD Signal and Visual Perception

Using fMRI and a psychophysical task involving letter identification, Kleinschmidt et al. (2002) (this issue of *Neuron*) delineate two patterns of neural activation, which manifest in different cortical regions: a transient activation, correlated with the change of a percept, and a longer-term hysteresis, correlated with the maintenance of the percept. These findings are provocative and suggest that neural hysteresis is mediated by visual structures that interact with higher-order regions to support longer-term maintenance of a percept.

One of the main advantages of functional magnetic resonance imaging (fMRI) is that it enables us to directly study the relationship between brain activation and explicit behavioral performance. The central contribution of the study by Kleinschmidt et al. (2002) is the differentiation of brain regions associated with perceptual awareness of a stimulus from regions associated with longer maintenance of the percept hysteresis. Perceptual hysteresis was induced by slowly increasing the contrast of a visual stimulus (letter) until its percept “popped out” and then gradually reducing the contrast until the percept “dropped out.” Subjects explicitly indicated via button press the times of pop out and drop out. Perceptual hysteresis was manifested in lower contrast levels at which drop out occurred compared to the contrast level at which pop out occurred.

Activity associated with subjects’ perceptual awareness of the stimuli was found in the inferior parietal, inferior frontal, and ventral lateral occipital cortical areas. These areas also exhibited priming-related effects, which were manifested in an earlier, reduced response during the second (compared to the first) exposure of each stimulus. Subsequent analysis of the fMRI signal

revealed clear evidence for neural hysteresis within the inferior parietal and inferior frontal regions; of note, this effect was only found during trials with perceptual hysteresis. Interestingly, the lateral occipital cortex (LOC) exhibited a more complex pattern of activity, reflecting its typical adaptation properties (Grill-Spector and Malach, 2001). In trials without perceptual hysteresis, a “reverse neural hysteresis” was found (i.e., stronger activation during contrast build-up than during contrast degradation). During the contrast-degrading phase, activity was stronger in trials with than without perceptual hysteresis, reflecting neural hysteresis indirectly. Finally, in contrast with the pattern observed in the areas discussed above, a region in the medial temporal cortex exhibited the reverse pattern of priming (i.e., an increase in activation during the second over the first exposure). The findings from this study raise two important issues: the relationship between neural hysteresis and visual awareness and the mechanisms mediating the hysteresis itself. We deal with each in turn.

Many previous studies point to ventral occipito-temporal visual areas as revealing a correlation between BOLD activation and subjects’ performance. It is the case, however, that some studies show enhancement of the signal following improvement in performance, while others show signal reduction. For example, Dolan et al. (1997) found enhancement of the BOLD signal in category-related ventral visual areas during a second exposure to displays containing degraded stimuli once the stimuli had become recognizable. Similarly, Grill-Spector et al. (2000) found enhancement of the BOLD signal for a set of briefly presented, masked stimuli on which subjects were intensively trained, compared to a novel set; furthermore, a correlation was found between BOLD activity and explicit recognition.

A seemingly conflicting line of evidence comes from a series of priming studies in which repeated presentation of a stimulus leads to improved object recognition but significant reduction in the fMRI signal (Buckner et al., 1998; Chao et al., 2002; Van Turrenout et al., 2000), reminiscent of the fMRI-adaptation phenomenon (Grill-Spector and Malach, 2001). Importantly, however, while different manipulations of face stimuli (position, size, and rotation) elicited differential adaptation effects in LOC, they elicited similar levels of performance, thus showing some deviation from a standard priming effect. Furthermore, fMRI signal reduction following priming has been shown to persist several days after the original event (Chao et al., 2002; Van Turrenout et al., 2000), a finding that cannot easily be attributed to adaptation processes that are typically short-lived.

At first glance, these studies reveal an apparent contradiction: both response increase and decrease are obtained as a function of behavioral improvement. How can this discrepancy be resolved? Two recent studies provide some explanation. Henson et al. (2000) report that repetition of familiar stimuli (faces or symbols) led to a signal reduction in a right fusiform region, while an enhanced response was found in this region following repetition of novel stimuli. Thus, familiarity may affect the extent of the fMRI signal following priming. Focusing on the temporal aspects of the recognition process, James et al. (2000) report a more complex interaction in which, during a precognition phase, primed objects